Exhibit I

FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS)
EMERGENCY USE AUTHORIZATION (EUA) OF THE MODERNA COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19)

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

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

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

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

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

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

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

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

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

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

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

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

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

DESCRIPTION OF COVID-19

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

DOSAGE AND ADMINISTRATION

Storage and Handling

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

During storage, minimize exposure to room light.

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

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

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

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

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

Thawed vials can be handled in room light conditions.

Do not refreeze once thawed.

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

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

Dosing and Schedule

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

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

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

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

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

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

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

Dose Preparation

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

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

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

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

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

Administer the Moderna COVID-19 Vaccine intramuscularly.

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

WARNINGS

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

AUTHORITY FOR ISSUANCE OF THE EUA

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

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

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

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

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

COUNTERMEASURES INJURY COMPENSATION PROGRAM

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

Moderna US, Inc.
Cambridge, MA 02139

©2021 ModernaTX, Inc. All rights reserved.
Patent(s): www.modernatx.com/patents
Revised: Oct/20/2021

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

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

MODERNA COVID-19 VACCINE

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

1 AUTHORIZED USE
2 DOSAGE AND ADMINISTRATION
2.1 Preparation for Administration
2.2 Administration
2.3 Dosing and Schedule
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Management of Acute Allergic Reactions
5.2 Myocarditis and Pericarditis
5.3 Syncope
5.4 Altered Immunocompetence
5.5 Limitations of Vaccine Effectiveness
6 OVERALL SAFETY SUMMARY
6.1 Clinical Trials Experience
6.2 Post-Authorization Experience
8 REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS
10 DRUG INTERACTIONS
11 USE IN SPECIFIC POPULATIONS
11.1 Pregnancy
11.2 Lactation
11.3 Pediatric Use
11.4 Geriatric Use
11.5 Use in Immunocompromised
13 DESCRIPTION
14 CLINICAL PHARMACOLOGY
14.1 Mechanism of Action
18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA
18.1 Efficacy of Two-Dose Primary Series
18.2 Immunogenicity in Solid Organ Transplant Recipients
18.3 Immunogenicity of a Booster Dose Following a Moderna COVID-19 Vaccine Primary Series
18.4 Immunogenicity of a Booster Dose Following Primary Vaccination with Another Authorized or Approved COVID-19 Vaccine
19 HOW SUPPLIED/STORAGE AND HANDLING
20 PATIENT COUNSELING INFORMATION
21 CONTACT INFORMATION

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

---

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

1 AUTHORIZED USE

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

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Preparation for Administration

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

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

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

2.2 Administration

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

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

Administer the Moderna COVID-19 Vaccine intramuscularly.

2.3 Dosing and Schedule

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

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

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

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

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

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

5.2 Myocarditis and Pericarditis

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

5.3 Syncope

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

5.4 Altered Immunocompetence

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

5.5 Limitations of Vaccine Effectiveness

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

6 OVERALL SAFETY SUMMARY

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

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

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

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

6.1 Clinical Trials Experience

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

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

Two-Dose Primary Series

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

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

Solicited Adverse Reactions

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

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

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

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

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

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

[a] Placebo was a saline solution.

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

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

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

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

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

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

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

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

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

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

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

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

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

Unsolicited Adverse Events

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

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

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

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

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

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

Serious Adverse Events

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

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

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

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

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

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

Solid Organ Transplant Recipients

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

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

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

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

Solicited Adverse Reactions

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

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

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

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

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

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

[b] Grade 3 erythema: Defined as >100 mm / >10 cm.

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

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

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

[f] Grade 3 fever: Defined as ≥39.0° – ≤40.0°C / ≥102.1° – ≤104.0°F.

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

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

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

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

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

Unsolicited Adverse Events

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

Serious Adverse Events

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

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

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

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

6.2 Post-Authorization Experience

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

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

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

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

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

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

*Serious Adverse Events are defined as:

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

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

Instructions for Reporting to VAERS

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

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

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

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

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

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

professional to contact about the adverse event.

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

Other Reporting Instructions

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

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

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

10 DRUG INTERACTIONS

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

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

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

postnatal development were reported in the study.

11.2 Lactation

Risk Summary

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

11.3 Pediatric Use

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

11.4 Geriatric Use

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

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

11.5 Use in Immunocompromised

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

13 DESCRIPTION

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

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

Moderna COVID-19 Vaccine does not contain a preservative.

The vial stoppers are not made with natural rubber latex.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

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

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

18.1 Efficacy of Two-Dose Primary Series

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

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

Efficacy Against COVID-19

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

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

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

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

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

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

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

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

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

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

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

18.2 Immunogenicity in Solid Organ Transplant Recipients

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

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

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

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

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

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

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

* Per-Protocol Immunogenicity Set included all subjects who had both baseline (or Study 2 Day 1 for Study 2) and post-vaccination immunogenicity samples, did not have SARS-CoV-2 infection at baseline (or Study 2 Day 1 for Study 2), did not have a major protocol deviation that impacted immune response, and had post-injection immunogenicity assessment at timepoint of primary interest (Day 29 for Study 2 and Day 57 for Study 1).
[a] Number of subjects with non-missing data at the corresponding timepoint.
[b] Given the lack of randomization in Study 2, the statistical analysis plan pre-specified an analysis of covariance model for estimating the geometric mean titer that adjusts for differences in age groups (<65 years, ≥65 years).
[c] Immunobridging is declared if the lower limit of the 2-sided 95% CI for the GMR is >0.67 and the point estimate of the GLSM ratio is ≥1.0.
Note: Antibody values < the lower limit of quantitation (LLOQ) are replaced by 0.5 × LLOQ. Values > the upper limit of quantitation (ULOQ) are replaced by the ULOQ if actual values are not available.
GLSM = Geometric least squares mean
GMR = Geometric mean ratio

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

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

* Per-Protocol Immunogenicity Set included all subjects who had both baseline (or Study 2 Day 1 for Study 2) and post-vaccination immunogenicity samples, did not have SARS-CoV-2 infection at baseline (or Study 2 Day 1 for Study 2), did not have a major protocol deviation that impacted immune response, and had post-injection immunogenicity assessment at timepoint of primary interest (Day 29 for Study 2 and Day 57 for Study 1).
[a] Seroresponse is defined as ≥4-fold rise of pseudovirus neutralizing antibody titers (ID50) from baseline (pre-booster dose in Study 2 and pre-dose 1 in Study 1), where baseline titers < LLOQ are set to LLOQ for the analysis.
[b] Number of subjects with non-missing data at both baseline and the post-baseline timepoint of interest.
[c] 95% CI is calculated using the Clopper-Pearson method.
[d] 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
[e] Immunobridging is declared if the lower limit of the 2-sided 95% CI for the percentage difference is > -10%.

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

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

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

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

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

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

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

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

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

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

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

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

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

19 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

During storage, minimize exposure to room light.

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

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

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

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

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

Thawed vials can be handled in room light conditions.

Do not refreeze once thawed.

<u>Transportation of Thawed Vials at 2° to 8°C (36° to 46°F)</u>

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

20 PATIENT COUNSELING INFORMATION

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

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

21 CONTACT INFORMATION

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

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

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

Moderna US, Inc.
Cambridge, MA 02139

©2021 ModernaTX, Inc. All rights reserved.
Patent(s): www.modernatx.com/patents
Revised: Oct/20/2021

Exhibit J

FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS)

EMERGENCY USE AUTHORIZATION (EUA) OF THE JANSSEN COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19)

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

SUMMARY OF INSTRUCTIONS FOR COVID-19 VACCINATION PROVIDERS

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

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

Primary Vaccination

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

Booster Dose

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

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

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

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

DESCRIPTION OF COVID-19

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

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

DOSAGE AND ADMINISTRATION

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

Storage and Handling

Storage Prior to First Puncture of the Vaccine Vial

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

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

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

Storage After First Puncture of the Vaccine Vial

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

Dosing and Schedule

Primary Vaccination

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

Booster Dose

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

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

Dose Preparation

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

Administration

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

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

Administer the Janssen COVID-19 Vaccine intramuscularly.

CONTRAINDICATION

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

WARNINGS

Management of Acute Allergic Reactions

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

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

Thrombosis with thrombocytopenia

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

Guillain-Barré Syndrome

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

Altered Immunocompetence

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

Syncope

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

Limitations of Vaccine Effectiveness

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

ADVERSE REACTIONS

Adverse Reactions in Clinical Trials

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

Adverse Reactions Identified during Post Authorization Use

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

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

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

USE WITH OTHER VACCINES

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

INFORMATION TO PROVIDE TO VACCINE RECIPIENTS/CAREGIVERS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Revised: Oct/20/2021

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

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

ADDITIONAL INFORMATION

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

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

AVAILABLE ALTERNATIVES

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

FEDERAL COVID-19 VACCINATION PROGRAM

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

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

AUTHORITY FOR ISSUANCE OF THE EUA

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

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

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

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

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

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

THE COUNTERMEASURES INJURY COMPENSATION PROGRAM

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

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

© 2021 Janssen Pharmaceutical Companies

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

Revised: Oct/20/2021

Revised: Oct/20/2021

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

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

1 AUTHORIZED USE
2 DOSAGE AND ADMINISTRATION
- 2.1 Preparation for Administration
- 2.2 Administration
- 2.3 Dosing and Schedule

3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
- 5.1 Management of Acute Allergic Reactions
- 5.2 Thrombosis with thrombocytopenia
- 5.3 Guillain-Barré Syndrome
- 5.4 Syncope
- 5.5 Altered Immunocompetence
- 5.6 Limitations of Vaccine Effectiveness

6 OVERALL SAFETY SUMMARY
- 6.1 Clinical Trials Experience
- 6.2 Post Authorization Experience

8 REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS
10 DRUG INTERACTIONS
11 USE IN SPECIFIC POPULATIONS
- 11.1 Pregnancy
- 11.2 Lactation
- 11.3 Pediatric Use
- 11.4 Geriatric Use

13 DESCRIPTION
14 CLINICAL PHARMACOLOGY
- 14.1 Mechanism of Action

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA
- 18.1 Efficacy of Primary Vaccination
- 18.2 Immunogenicity of a Booster Dose following Primary Vaccination with Janssen COVID-19 Vaccine
- 18.3 Immunogenicity of a Booster Dose Following Primary Vaccination with Another Authorized or Approved COVID-19 Vaccine

19 HOW SUPPLIED/STORAGE AND HANDLING
20 PATIENT COUNSELING INFORMATION
21 CONTACT INFORMATION

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

Revised: Oct/20/2021

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

1 AUTHORIZED USE

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

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Preparation for Administration

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

2.2 Administration

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

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

Administer the Janssen COVID-19 Vaccine intramuscularly.

2.3 Dosing and Schedule

Primary Vaccination

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

Booster Dose

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

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

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

5.2 Thrombosis with thrombocytopenia

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

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

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

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

5.3 Guillain-Barré Syndrome

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

5.4 Syncope

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

5.5 Altered Immunocompetence

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

5.6 Limitations of Vaccine Effectiveness

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

6 OVERALL SAFETY SUMMARY

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

Adverse Reactions in Clinical Trials

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

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

Adverse Reactions Identified during Post Authorization Use

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

6.1 Clinical Trials Experience

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

Safety Primary vaccination

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

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

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

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

Solicited adverse reactions

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Unsolicited adverse events

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

Serious Adverse Events (SAEs) and other events of interest

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

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

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

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

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

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

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

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

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

Booster Dose Following Primary Vaccination with Janssen COVID-19 Vaccine

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

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

Solicited adverse reactions

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Unsolicited adverse events

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

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

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

6.2 Post Authorization Experience

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

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

Cardiac disorders: Myocarditis, Pericarditis.

Ear and labyrinth disorders: Tinnitus.

Gastrointestinal disorders: Diarrhea, Vomiting.

Immune System Disorders: Allergic reactions, including anaphylaxis.

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

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

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

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

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

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

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

Instructions for Reporting to VAERS

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

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

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

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

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

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

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

Other Reporting Instructions

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

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

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

10 DRUG INTERACTIONS

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

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

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

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

11.2 Lactation

Risk Summary

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

11.3 Pediatric Use

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

11.4 Geriatric Use

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

13 DESCRIPTION

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

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

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

Janssen COVID-19 Vaccine does not contain a preservative.

The vial stoppers are not made with natural rubber latex.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

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

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

18.1 Efficacy of Primary Vaccination

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

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

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

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

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

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

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

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

Efficacy Against COVID-19

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

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

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

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

Primary analysis

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

LLOQ = lower limit of quantification

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

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

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

19 HOW SUPPLIED/STORAGE AND HANDLING

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

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

Storage Prior to First Puncture of the Vaccine Vial

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

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

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

Storage After First Puncture of the Vaccine Vial

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

20 PATIENT COUNSELING INFORMATION

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

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

21 CONTACT INFORMATION

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

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

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

Revised: Oct/20/2021

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

Revised: Oct/20/2021
© 2021 Janssen Pharmaceutical Companies

Exhibit K

U.S. FOOD & DRUG ADMINISTRATION

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

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

Dear Mr. Patel:

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

LICENSING

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

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

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

MANUFACTURING LOCATIONS

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

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

DATING PERIOD

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

FDA LOT RELEASE

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

BIOLOGICAL PRODUCT DEVIATIONS

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

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

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

MANUFACTURING CHANGES

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

LABELING

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

CONTENT OF LABELING

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

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELS

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

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

ADVERTISING AND PROMOTIONAL LABELING

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

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

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

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

ADVERSE EVENT REPORTING

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

PEDIATRIC REQUIREMENTS

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

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

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

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

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

   Final Protocol Submission: October 7, 2020

   Study Completion: May 31, 2023

   Final Report Submission: October 31, 2023

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

   Final Protocol Submission: February 8, 2021

   Study Completion: November 30, 2023

   Final Report Submission: May 31, 2024

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

   Final Protocol Submission: January 31, 2022

   Study Completion: July 31, 2024

   Final Report Submission: October 31, 2024

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

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

- **Required Pediatric Assessment(s)**

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

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

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

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

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

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

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

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

   Final Protocol Submission: August 31, 2021

   Monitoring Report Submission: October 31, 2022

   Interim Report Submission: October 31, 2023

   Study Completion: June 30, 2025

   Final Report Submission: October 31, 2025

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

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

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

Final Protocol Submission: August 11, 2021

Progress Report Submission: September 30, 2021

Interim Report 1 Submission: March 31, 2022

Interim Report 2 Submission: September 30, 2022

Interim Report 3 Submission: March 31, 2023

Interim Report 4 Submission: September 30, 2023

Interim Report 5 Submission: March 31, 2024

Study Completion: March 31, 2024

Final Report Submission: September 30, 2024

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

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

   Final Protocol Submission: January 31, 2022

   Study Completion: March 31, 2024

   Final Report Submission: September 30, 2024

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

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

   Final Protocol Submission: November 30, 2021

   Study Completion: December 31, 2026

Final Report Submission: May 31, 2027

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

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

   Final Protocol Submission: September 30, 2021

   Study Completion: November 30, 2023

   Final Report Submission: May 31, 2024

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

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

   Final Protocol Submission: November 30, 2021

   Study Completion: June 30, 2022

   Final Report Submission: December 31, 2022

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

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

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

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

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

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

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

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

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

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

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

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

    Final Protocol Submission: July 1, 2021

Study Completion: June 30, 2025

Final Report Submission: December 31, 2025

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

    Final Protocol Submission: September 30, 2021

    Study Completion: November 30, 2023

    Final Report Submission: May 31, 2024

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

    Final Protocol Submission: January 29, 2021

    Study Completion: June 30, 2023

    Final Report Submission: December 31, 2023

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

    Final Protocol Submission: March 22, 2021

    Study Completion: December 31, 2022

    Final Report Submission: June 30, 2023

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

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

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

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

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

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

POST APPROVAL FEEDBACK MEETING

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

Sincerely,

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

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

Exhibit L

U.S. FOOD & DRUG ADMINISTRATION

September 22, 2021

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

Dear Mr. Patel:

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

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

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

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

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

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

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

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

---

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

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

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

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

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

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

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

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

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

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

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

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

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

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

I. Criteria for Issuance of Authorization

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

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

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

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

II. Scope of Authorization

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

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

---

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

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

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

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

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

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

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

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

Product Description[17]

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

---

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

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

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

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

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

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

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

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

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

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

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

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

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

III. Conditions of Authorization

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

<u>Pfizer Inc. and Authorized Distributor(s)</u>

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

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

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

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

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

D. Pfizer Inc. may develop and disseminate instructional and educational materials (e.g., video regarding vaccine handling, storage/cold-chain management, preparation, disposal) that are consistent with the authorized emergency use of the vaccine as described in the letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs during an emergency. Any instructional and educational materials that are inconsistent with the authorized labeling are prohibited.

E. Pfizer Inc. may request changes to this authorization, including to the authorized Fact Sheets for the vaccine. Any request for changes to this EUA must be submitted to Office of Vaccines Research and Review (OVRR)/Center for Biologics Evaluation and Research (CBER). Such changes require appropriate authorization prior to implementation.[19]

F. Pfizer Inc. will report to Vaccine Adverse Event Reporting System (VAERS):
   - Serious adverse events (irrespective of attribution to vaccination);
   - Cases of Multisystem Inflammatory Syndrome in children and adults; and
   - Cases of COVID-19 that result in hospitalization or death, that are reported to Pfizer Inc.

   These reports should be submitted to VAERS as soon as possible but no later than 15 calendar days from initial receipt of the information by Pfizer Inc.

G. Pfizer Inc. must submit to Investigational New Drug application (IND) number 19736 periodic safety reports at monthly intervals in accordance with a due date agreed upon with the Office of Biostatistics and Epidemiology (OBE)/CBER beginning after the first full calendar month after authorization. Each periodic safety report is required to contain descriptive information which includes:
   - A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest;
   - A narrative summary and analysis of vaccine administration errors, whether or not associated with an adverse event, that were identified since the last reporting interval;
   - Newly identified safety concerns in the interval; and

[19] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), or (7), review and concurrence is required from the Preparedness and Response Team (PREP)/Office of the Center Director (OD)/CBER and the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS).

- Actions taken since the last report because of adverse experiences (for example, changes made to Healthcare Providers Administering Vaccine (Vaccination Providers) Fact Sheet, changes made to studies or studies initiated).

H. No changes will be implemented to the description of the product, manufacturing process, facilities, or equipment without notification to and concurrence by FDA.

I. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.

J. Pfizer Inc. will submit to the EUA file Certificates of Analysis (CoA) for each drug product lot at least 48 hours prior to vaccine distribution. The CoA will include the established specifications and specific results for each quality control test performed on the final drug product lot.

K. Pfizer Inc. will submit to the EUA file quarterly manufacturing reports, starting in July 2021, that include a listing of all Drug Substance and Drug Product lots produced after issuance of this authorization. This report must include lot number, manufacturing site, date of manufacture, and lot disposition, including those lots that were quarantined for investigation or those lots that were rejected. Information on the reasons for lot quarantine or rejection must be included in the report.

L. Pfizer Inc. and authorized distributor(s) will maintain records regarding release of Pfizer-BioNTech COVID-19 Vaccine for distribution (i.e., lot numbers, quantity, release date).

M. Pfizer Inc. and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

N. Pfizer Inc. will conduct post-authorization observational studies to evaluate the association between Pfizer-BioNTech COVID-19 Vaccine and a pre-specified list of adverse events of special interest, including myocarditis and pericarditis, along with deaths and hospitalizations, and severe COVID-19. The study population should include individuals administered the authorized Pfizer-BioNTech COVID-19 Vaccine under this EUA in the general U.S. population (12 years of age and older), individuals that receive a booster dose, populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, subpopulations with specific comorbidities. The studies should be conducted in large scale databases with an active comparator. Pfizer Inc. will provide protocols and status update reports to the IND 19736 with agreed-upon study designs and milestone dates.

<u>Emergency Response Stakeholders</u>

O. Emergency response stakeholders will identify vaccination sites to receive authorized Pfizer-BioNTech COVID-19 Vaccine and ensure its distribution and administration, consistent with the terms of this letter and CDC's COVID-19 Vaccination Program.

P. Emergency response stakeholders will ensure that vaccination providers within their jurisdictions are aware of this letter of authorization, and the terms herein and any subsequent amendments that might be made to the letter of authorization, instruct them about the means through which they are to obtain and administer the vaccine under the EUA, and ensure that the authorized labeling [i.e., Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and Vaccine Information Fact Sheet for Recipients and Caregivers] is made available to vaccination providers through appropriate means (e.g., e-mail, website).

Q. Emergency response stakeholders receiving authorized Pfizer-BioNTech COVID-19 Vaccine will ensure that appropriate storage and cold chain is maintained.

Vaccination Providers

R. Vaccination providers will administer the vaccine in accordance with the authorization and will participate and comply with the terms and training required by CDC's COVID-19 Vaccination Program.

S. Vaccination providers will provide the Vaccine Information Fact Sheet for Recipients and Caregivers to each individual receiving vaccination and provide the necessary information for receiving their second dose and/or third dose.

T. Vaccination providers administering the vaccine must report the following information associated with the administration of the vaccine of which they become aware to VAERS in accordance with the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers):
   - Vaccine administration errors whether or not associated with an adverse event
   - Serious adverse events (irrespective of attribution to vaccination)
   - Cases of Multisystem Inflammatory Syndrome in children and adults
   - Cases of COVID-19 that result in hospitalization or death

   Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. The VAERS reports should include the words "Pfizer-BioNTech COVID-19 Vaccine EUA" in the description section of the report. More information is available at vaers.hhs.gov or by calling 1-800-822-7967. To the extent feasible, report to Pfizer Inc. by contacting 1-800-438-1985 or by providing a copy of the VAERS form to Pfizer Inc.; Fax: 1-866-635-8337.

U. Vaccination providers will conduct any follow-up requested by the U.S government, including CDC, FDA, or other designee, regarding adverse events to the extent feasible given the emergency circumstances.

V. Vaccination providers will monitor and comply with CDC and/or emergency response stakeholder vaccine management requirements (e.g., requirements

concerning obtaining, tracking, and handling vaccine) and with requirements concerning reporting of vaccine administration data to CDC.

W. Vaccination providers will ensure that any records associated with this EUA are maintained until notified by FDA. Such records will be made available to CDC, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising, and Promotion

X. All descriptive printed matter, advertising, and promotional material, relating to the use of the Pfizer-BioNTech COVID-19 Vaccine shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in section 502(a) and (n) of the FD&C Act and FDA implementing regulations.

Y. All descriptive printed matter, advertising, and promotional material relating to the use of the Pfizer-BioNTech COVID-19 Vaccine clearly and conspicuously shall state that:
- This product has not been approved or licensed by FDA, but has been authorized for emergency use by FDA, under an EUA to prevent Coronavirus Disease 2019 (COVID-19) for use in individuals 12 years of age and older; and
- The emergency use of this product is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of the medical product under Section 564(b)(1) of the FD&C Act unless the declaration is terminated or authorization revoked sooner.

Condition Related to Export

Z. If the Pfizer-BioNTech COVID-19 Vaccine is exported from the United States, conditions C, D, and O through Y do not apply, but export is permitted only if 1) the regulatory authorities of the country in which the vaccine will be used are fully informed that this vaccine is subject to an EUA and is not approved or licensed by FDA and 2) the intended use of the vaccine will comply in all respects with the laws of the country in which the product will be used. The requirement in this letter that the authorized labeling (i.e., Fact Sheets) be made available to vaccination providers, recipients, and caregivers in condition A will not apply if the authorized labeling (i.e., Fact Sheets) are made available to the regulatory authorities of the country in which the vaccine will be used.

Conditions With Respect to Use of Licensed Product

AA. COMIRNATY (COVID-19 Vaccine, mRNA) is now licensed for individuals 16 years of age and older. There remains, however, a significant amount of Pfizer-BioNTech COVID-19 Vaccine that was manufactured and labeled in accordance with this emergency use authorization. The authorization remains in place with respect to the Pfizer-BioNTech COVID-19 Vaccine.

BB. This authorization also covers the use of the licensed COMIRNATY (COVID-19 Vaccine, mRNA) product when used to provide: a two-dose regimen for individuals aged 12 through 15 years; a third dose to individuals 12 years of age or older who have undergone solid organ transplantation or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise; or a single booster dose at least 6 months after completing the primary series to individuals: 65 years of age or older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19. Conditions A through W in this letter apply when COMIRNATY (COVID-19 Vaccine, mRNA) is provided for the uses described in this subsection III.BB, except that product manufactured and labeled in accordance with the approved BLA is deemed to satisfy the manufacturing, labeling, and distribution requirements of this authorization.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures

Exhibit M

Summary Basis for Regulatory Action

Date:	08/23/2021
From:	Ramachandra Naik, PhD, Review Committee Chair, DVRPA/OVRR
BLA STN:	125742/0
Applicant:	BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.)
Submission Receipt Date:	May 18, 2021
PDUFA Action Due Date:	January 16, 2022
Proper Name:	COVID-19 Vaccine, mRNA
Proprietary Name:	COMIRNATY
Indication:	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older

Recommended Action: The Review Committee recommends approval of this product.

_____

Director, Office of Vaccines Research and Review

_____

Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (OVRR) • Facilities Review (OCBQ/DMPQ) • Facilities Inspection (OCBQ/DMPQ and OVRR/DVP) • Lot Release, QC, Test Methods, Product Quality (OCBQ/DBSQC)	Xiao Wang, PhD, OVRR/DVP Anissa Cheung, MSc, OVRR/DVP Kathleen Jones, PhD, OCBQ/DMPQ Laura Fontan, PhD, OCBQ/DMPQ Gregory Price, PhD, OCBQ/DMPQ CDR Donald Ertel, MS, OCBQ/DMPQ Nicole Li, MS, OCBQ/DMPQ Christian Lynch, OCBQ/DMPQ Alifiya Ghadiali, OCBQ/DMPQ Zhongren Wu, PhD, OCBQ/DMPQ Ekaterina Allen, PhD, OCBQ/DMPQ Hsiaoling Wang, PhD, OCBQ/DBSQC Emnet Yitbarek, PhD, OCBQ/DBSQC Karla Garcia, MS, OCBQ/DBSQC Anil Choudhary, PhD, MBA, OCBQ/DBSQC Esmeralda Alvarado Facundo, PhD, OCBQ/DBSQC Marie Anderson, PhD, OCBQ/DBSQC Cheryl Hulme, OCBQ/DMPQ
Clinical • Clinical (OVRR) • Postmarketing Safety, Epidemiological Review (OBE/DE) • Real World Evidence • Benefit-Risk Assessment • BIMO	Susan Wollersheim, MD, OVRR/DVRPA CAPT Ann T. Schwartz, MD, OVRR/DVRPA Lucia Lee, MD, OVRR/DVRPA Deborah Thompson, MD, MSPH, OBE/DE Yun Lu, PhD, OBE Hong Yang, PhD, OBE Osman Yogurtcu, PhD, OBE Patrick Funk, PhD, OBE Haecin Chun, MT (ASCP) SSB, MS, OCBQ/DIS
Statistical • Clinical Data (OBE/DB) • Nonclinical Data	Lei Huang, PhD, OBE/DB Ye Yang, PhD, OBE/DB Xinyu Tang, PhD, OBE/DB
Nonclinical/Pharmacology/Toxicology • Toxicology (OVRR) • Developmental Toxicology (OVRR)	Nabil Al-Humadi, PhD, OVRR/DVRPA
Labeling • Promotional (OCBQ/APLB) • Carton and Container Labels • Labeling Review	CAPT Oluchi Elekwachi, PharmD, MPH, OCBQ/APLB Daphne Stewart, OVRR/DVRPA Laura Gottschalk, PhD, OVRR/DVRPA
• Consults (CDISC, Datasets) • Documentation Review	Brenda Baldwin, PhD, OVRR/DVRPA CAPT Michael Smith, PhD, OVRR/DVRPA
Advisory Committee Summary	No Advisory Committee meeting held

Table of Contents

1. Introduction 3
2. Background 4
3. Chemistry, Manufacturing and Controls (CMC) 6
   a. Product Quality 6
   b. Testing Specifications 10
   c. CBER Lot Release 11
   d. Facilities Review / Inspection 11
   e. Container/Closure System 14
   f. Environmental Assessment 14
4. Nonclinical Pharmacology/Toxicology 14
5. Clinical Pharmacology 15
6. Clinical/Statistical 15
   a. Clinical Program 15
   b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance ... 22
7. Safety and Pharmacovigilance 22
8. Labeling 25
9. Advisory Committee Meetings 26
10. Other Relevant Regulatory Issues 27
11. Recommendations and Benefit/Risk Assessment 27
   a. Recommended Regulatory Action 27
   b. Benefit/Risk Assessment 28
   c. Recommendation for Postmarketing Activities 28

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:

(b) (4)

Drug Product (DP)

The manufacturing process of the DP is divided into the following critical steps:

- **Preparation of the DS:** (b) (4)
- **Formation of LNP:** In this step, (b) (4) .
- **Formulation of the bulk DP:** The bulk DP is formulated by (b) (4)
- **Filling:** The bulk DP is sterile filtered and aseptically filled into 2 mL Type I borosilicate glass vials manufactured by (b) (4)
- **Labeling and storage:** The filled vials are visually inspected, labeled, and frozen at -90°C to -60°C.

Composition

The composition of the formulation of COMIRNATY and the function of the ingredients are provided in Table 2.

Table 2. Composition of COMIRNATY Multiple Dose Vial

Ingredients	**Quantity after Dilution (per vial)**	**Function**
SARS-CoV-2 spike glycoprotein mRNA (UNII: 5085ZFP6SJ)	225 µg	Active Ingredient
ALC-0315 [4-hydroxybutyl)azanediyl)bis (hexane-6,1-diyl)bis(2-hexyldecanoate) (UNII: AVX8DX713V)	3.23 mg	Lipid component
ALC-0159 [2-(polyethylene glycol 2000)-N,N-ditetradecylacetamide] (UNII: PJH39UMU6H)	0.4 mg	Lipid component
DSPC [1,2-distearoyl-sn-glycero-3-phosphocholine] (UNII: 043IPI2M0K)	0.7 mg	Lipid component
Cholesterol (UNII: 97C5T2UQ7J)	1.4 mg	Lipid component
Potassium chloride (UNII: 660YQ98I10)	0.07 mg	Excipient
Monobasic potassium phosphate (UNII: 4J9FJ0HL51)	0.07 mg	Excipient
Sodium Chloride	2.7 mg	Excipient

Ingredients	Quantity after Dilution (per vial)	Function
(UNII: 451W47IQ8X)		
Dibasic sodium phosphate dihydrate (UNII: GR686LBA74)	0.49 mg	Excipient
Sucrose (UNII: C151H8M554)	46.0 mg	Excipient
Water for Injection (UNII: 059QF0KO0R)	0.450 mL	Excipient

UNII: Unique Ingredient Identifier

Stability of COMIRNATY in Multiple Dose Vial

For the long-term storage condition study, parameters monitored are Appearance, (b) (4) by (b) (4) LNP (b) (4) (b) (4) RNA content and (b) (4) (b) (4) Assay, Lipid (ALC-0315, ALC-0159, DSPC, and Cholesterol) Content by (b) (4) , Container closure integrity test by (b) (4) (b) (4) Endotoxin content by (b) (4) , and Sterility.

The stability data provided in the submission support a dating period of 9 months from the date of manufacture when stored at -90°C to -60°C for the COMIRNATY DP filled in 2 mL Type I borosilicate glass vials. Stability data on emergency use and process performance qualification lots also support storage at -20°C ± 5°C for up to 2 weeks as well as short term storage at 5°C ± 3°C for up to one month (within the 9-month expiry dating period).

The Diluent for COMIRNATY

The contents of the vaccine vial are diluted with sterile 0.9% Sodium Chloride Injection, USP. Vials of sterile 0.9% Sodium Chloride Injection, USP are provided but shipped separately. The provided diluent or another sterile 0.9% Sodium Chloride Injection, USP should be used as the diluent.

The provided 0.9% Sodium Chloride Injection, USP diluent will be supplied either as cartons of 10 mL single-use vials manufactured by Hospira, Inc (NDC 0409-4888-10), or 2 mL single-use vials manufactured by Fresenius Kabi USA, LLC (NDC 63323-186-02). The composition of the saline diluent and the function of the ingredients are provided in Table 3.

Table 3. Composition of the Diluent

Ingredients	Quantity (per 0.3 mL dose)	Function
SODIUM CHLORIDE (UNII: 451W47IQ8X)	2.16 mg	Excipient
Water for Injection (UNII: 059QF0KO0R)	0.3 mL	Excipient

UNII: Unique Ingredient Identifier

COMIRNATY

Product Composition

COMIRNATY Multiple Dose Vial is supplied as a frozen suspension that is diluted at the time of use with 1.8 mL of saline diluent. A single dose of COMIRNATY contains 30 ug mRNA in a volume of 0.3 mL, and it does not contain preservative. [*See section 10.b regarding exception to the 21 CFR 610.15(a) requirement for a preservative.*]

Stability of COMIRNATY

The Applicant conducted in-use stability studies to support the maximum temperature and time period that COMIRNATY can retain its physicochemical properties. Based on the data generated, COMIRNATY retains its quality attributes for up to 6 hours when stored between 2°C to 25°C (35°F to 77°F).

The carton labels and the Package Insert (PI) state that after dilution, vials should be stored between 2°C to 25°C (35°F to 77°F) and used within 6 hours from the time of dilution. During storage, exposure to room light should be minimized, and direct exposure to sunlight and ultraviolet light should be avoided. Any vaccine remaining in vials must be discarded after 6 hours and cannot be refrozen.

Assays used in clinical studies

Diagnostic Assays Used to Support Clinical Efficacy Endpoints

Two clinical diagnostic assays (Cepheid Xpert Xpress RT-PCR assay for the detection of SARS-CoV-2 in clinical specimens and Roche Elecsys Anti-SARS-CoV-2 assay for the evaluation of serostatus to SARS-CoV-2) were used to assess clinical endpoints. Both assays have received FDA authorization under EUA.

The Cepheid Xpert Xpress RT-PCR assay is a rapid, automated *in vitro* diagnostic test for the qualitative detection of the N and E gene sequences from nasopharyngeal, nasal, or mid-turbinate swab and/or nasal wash/aspirate specimens collected from patients suspected of having COVID-19. This assay is used to assess viral infection of the participants before vaccination and to confirm COVID-19 cases during study follow-up.

The Roche Elecsys Anti-SARS-CoV-2 assay is a rapid, automated *in vitro* diagnostic test for detecting the presence of antibodies to nucleocapsid (N) protein of SARS-CoV-2 (antigen not present in COMIRNATY) in serum or plasma samples. This is a qualitative assay marketed as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2, which would indicate a recent or prior infection. This assay is used to assess serostatus of the participants before vaccination.

Data were submitted to support the suitability of both the Cepheid Xpert Xpress assay and the Roche Elecsys Anti-SARS-CoV-2 assay for their intended uses in Phase 2/3 clinical studies when performed at Pfizer's testing facility (Pfizer Vaccine Research and Development; Pearl River, NY).

Immunogenicity Assays Used for Exploratory Immunogenicity Endpoints

Two immunogenicity assays (SARS-CoV-2 mNeonGreen (mNG) virus microneutralization assay and (b) (4) direct Luminex assay (dLIA) for IgG

quantification) were used for evaluating the immune responses from clinical trial samples.

The SARS-CoV-2 mNG microneutralization assay measures neutralizing antibodies (50% inhibition titers) against SARS-CoV-2 using Vero cell monolayers in a 96-well plate format. The SARS-CoV-2 mNG virus is derived from the USA_WA1/2020 strain that had been rescued by reverse genetics and engineered to express a fluorescent reporter gene (mNeonGreen) upon productive infection of cells. The validation protocol (that includes evaluation of dilutional linearity, precision, limits of quantification, and limit of detection) and the results of the validation study, executed at Pfizer Hackensack Meridian Health Center (Nutley, New Jersey), were submitted to support the suitability of the assay for testing of clinical trial immunogenicity samples.

The (b) (4) S1 IgG dLIA measures IgG antibody levels to the subunit 1 (S1) of the SARS-CoV-2 spike protein in human serum samples. Qualification data provided in the submission support the (b) (4) dLIA for quantification of human IgG antibodies that bind to the S1 protein of SARS-CoV-2 and confirm that the assay is suitable for its intended use.

b. Testing Specifications

Specifications and Methods

The tests and specifications applied for routine release of COMIRNATY are shown in Table 4.

Table 4. Control of COMIRNATY: Tests and Specifications

Quality Attribute	Analytical Procedure	Acceptance Criteria
Appearance	Appearance (Visual)	White to off-white suspension
Appearance (Visible Particulates)	Appearance (Particles) (b) (4))	May contain white to off-white opaque, amorphous particles
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4) (b) (4)	(b) (4)
(b) (4)	(b) (4) (b) (4)	(b) (4)
LNP (b) (4)	(b) (4))	(b) (4)
LNP (b) (4)	(b) (4))	(b) (4)
RNA (b) (4)	(b) (4) assay	(b) (4)
RNA content	(b) (4) assay	(b) (4)
ALC-0315 content	(b) (4)	(b) (4)
ALC-0159 content	(b) (4)	(b) (4)
DSPC content	(b) (4)	(b) (4)
Cholesterol content	(b) (4)	(b) (4)
Vial content (volume)	Container content	Not less than (b) (4)
Lipid identities	(b) (4)	(b) (4) (ALC-0315, ALC-0159, Cholesterol, DSPC)

Quality Attribute	Analytical Procedure	Acceptance Criteria
Identity of encoded RNA	(b) (4)	Identity confirmed
(b) (4)	(b) (4)	(b) (4)
RNA (b) (4)	(b) (4)	(b) (4))
Bacterial Endotoxin	Endotoxin ((b) (4) (b) (4)	(b) (4)
Sterility	Sterility ((b) (4))	No Growth Detected
Container Closure Integrity	(b) (4)	Pass

Abbreviations: LNP = Lipid nanoparticles (b) (4)

The analytical methods and their validations and/or qualifications for the COMIRNATY DS and DP were found to be adequate for their intended use.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of COMIRNATY are listed in Table 5 below. The activities performed and inspectional histories are also noted in Table 5 and are further described in the paragraphs that follow.

Table 5. Facilities involved in the manufacture of COMIRNATY

Name/address	FEI Number	DUNS number	Inspection/ waiver	Results/ Justification
Pfizer Inc. 875 Chesterfield Parkway West Chesterfield, MO 63017 (b) (4) Manufacture *Drug Substance* Release and stability testing *Drug Product* Release and stability testing	1940118	004954111	Waiver	ORA Surveillance August 19-20, 2019 NAI
Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC 1 Burtt Road Andover, MA 01810 *Drug Substance* Manufacture, release and stability testing *Drug Product* Release and stability testing	1222181	174350868	Pre-License Inspection	CBER Pre-license inspection July 19-23, 2021 VAI
Pharmacia & Upjohn Company LLC 7000 Portage Road Kalamazoo, MI 49001 *Drug Product* LNP production, bulk drug product formulation, fill and finish, primary packaging, secondary packaging, release and stability testing	1810189	618054084	Waiver	ORA/OBPO Surveillance May 11-20, 2021 VAI
Pfizer Manufacturing Belgium NV Rijksweg 12 Puurs, 2870 Belgium *Drug Product* LNP production, bulk drug product formulation, fill and finish, primary packaging, secondary packaging, release and stability testing	1000654629	370156507	Pre-license inspection	CBER Pre-license inspection June 24-July 2, 2021 NAI

Name/address	FEI Number	DUNS number	Inspection/ waiver	Results/ Justification
Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin, Dublin 22 Ireland *Drug Product* Release and stability testing	3004145594	985586408	Waiver	ORA Surveillance November 4-12, 2019 VAI
(b) (4) *Drug Product* Release testing (sterility)	(b) (4)	(b) (4)	Waiver	CDER Pre-approval inspection (b) (4) VAI
(b) (4) *Drug Product* Release testing (sterility)	(b) (4)	(b) (4)	Waiver	ORA Surveillance (b) (4) VAI

ORA conducted a surveillance inspection of Pfizer Inc., Chesterfield, MO, from August 19 – 20, 2019. No Form FDA 483 was issued, and the inspection was classified as No Action Indicated (NAI).

CBER conducted a pre-license inspection (PLI) of Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC from July 19 – 23, 2021. All inspectional issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

ORA conducted a surveillance inspection of Pharmacia & Upjohn Company LLC from May 11 – 20, 2021. All inspectional issues were resolved, and the inspection was classified as VAI.

CBER conducted a PLI of Pfizer Manufacturing Belgium NV from June 24 - July 2, 2021. No Form FDA 483 was issued, and the inspection was classified as NAI.

ORA conducted a surveillance inspection of Pfizer Ireland Pharmaceuticals from November 4 – 12, 2019. All inspectional issues were resolved, and the inspection was classified as VAI.

CDER conducted a pre-approval inspection of (b) (4) from (b) (4) (b) (4) . All inspectional issues were resolved, and the inspection was classified as VAI.

ORA conducted a surveillance inspection of (b) (4) from (b) (4) (b) (4) . All inspectional issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The COMIRNATY drug product is filled and stored at -90°C to -60°C in a 2 mL glass vial sealed with a bromobutyl rubber stopper and an aluminum seal with flip-off plastic cap. The glass vials are supplied by (b) (4) The stopper and caps are supplied by (b) (4) (b) (4) , respectively.

Pfizer performed container closure integrity testing (CCIT) on the filled 2 mL glass vials using a (b) (4) test method. All acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

Nonclinical Toxicology

For the nonclinical safety evaluation, COMIRNATY was evaluated in two repeat dose toxicity studies in Wistar Han rats and a Combined Fertility and Developmental Study (Including Teratogenicity and Postnatal Investigations) in Wistar Han rats.

The repeat dose toxicity evaluations were conducted on COMIRNATY and a similar vaccine termed BNT162b2 (V8). COMIRNATY and BNT162b2 (V8) have identical amino acid sequences of the encoded antigens but COMIRNATY includes the presence of optimized codons to improve antigen expression. The IM route of exposure was selected as it is the route of clinical administration. Generation of an immune response to COMIRNATY was confirmed in rats in both repeat-dose toxicity studies. In both repeat-dose toxicity studies, administration of COMIRNATY by IM injection to male and female rats once every week for a total of 3 doses was tolerated without evidence of systemic toxicity. Edema and erythema at the injection sites, transient elevation in body temperature, elevations in white blood cells and acute phase reactants and decreased albumin:globulin ratios were observed. Injection site reactions were common in all vaccine-administered animals and were greater after boost immunizations.

For the Combined Fertility and Developmental Study, COMIRNATY was administered to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 µg RNA/dosing day). There were some effects (change in body weight and food consumption and effects localized to the injection site) observed in rats in these studies following administration of COMIRNATY that were not considered adverse and a relationship to COMIRNATY was not established. There were no effects on mating performance, fertility, or any ovarian or uterine parameters nor on embryo-fetal or postnatal survival, growth, or development in the offspring. An immune response was observed in female rats following administration of each vaccine candidate and these responses were also detectable in the offspring (fetuses and pups).

Nonclinical Pharmacology and Pharmacokinetics
COMIRNATY was evaluated in nonclinical pharmacology studies using animal models of mice, rats and nonhuman primates (NHP). The data from these studies indicate: (1) strong antigen-binding IgG and high titer neutralizing antibodies in mice, rat and rhesus macaques; (2) Th1-biased CD4+ T-cell response and IFNγ+, CD8+ T-cell response to BNT162b2 in both mouse and NHP studies; and (3) protection of rhesus macaques from an infectious SARS-CoV-2 challenge, with reduced detection of viral RNA in the BNT162b2-immunized animals as compared with the control-immunized macaques.

Nonclinical pharmacokinetics (PK) evaluation included (1) biodistribution of COMIRNATY using (b) (4) expressing RNA as a surrogate reporter in (b) (4) mice and in rats, and (2) the biodistribution and metabolism of the two novel lipids (ALC-0315 and ALC-0159) contained in COMIRNATY in *in vitro* studies and in a PK study in rats following administration of (b) (4) expressing RNA encapsulated in LNPs made with radiolabeled lipid markers. The study results indicate that following IM injection, the RNA encapsulated in LNP mainly localizes to the site of injection and, to a lesser extent, distributes to the liver. The metabolism of ALC-0315 and ALC-0159 was evaluated *in vitro* using blood, liver microsomes, S9 fractions, and hepatocytes from mice, rats, monkeys and humans and in *vivo* by examining the plasma, urine, feces, and liver samples from the PK study in rats. Approximately 50% of ALC-0159 is excreted unchanged in feces, while metabolism appears to play a role in the elimination of ALC-0315.

5. Clinical Pharmacology

Pharmacodynamic data, comprised of humoral immune responses to COMIRNATY, were obtained in the clinical studies. The data demonstrated that COMIRNATY induces a humoral immune response against the SARS-CoV-2 spike protein. The exact immunologic mechanism that confers protection against SARS-CoV-2 is unknown.

6. Clinical/Statistical

a. Clinical Program

Overview
The Applicant included data from two clinical studies in the BLA. The clinical studies which will be discussed in this SBRA are shown in Table 6.

Table 6. Overview of Clinical Studies

Study ID	**C4591001**	**BNT162-01**
NCT ID	04368728	04380701
Phase	1/2/3	1/2
Countries	Argentina, Brazil, Germany, South Africa, Turkey, U.S.	Germany
Enrollment	Phase 1: 30 participants Phase 2/3: 43,847 participants	24
Age	16 - 85 YOA	18 - 85 YOA
Purpose	Evaluate VE for prevention of COVID-19 (pivotal clinical endpoint study)	Evaluate safety and immunogenicity

Study ID	C4591001	BNT162-01
Control	Saline Placebo	None
Groups	Phase 2/3: 2 groups, randomized 1:1 to receive COMIRNATY or Placebo IM	1 group, randomized received COMIRNATY IM
Schedule	D0, D21	D0, D21
Total follow-up	6 Months (follow-up ongoing)	6 Months (follow-up ongoing)

YOA: years of age; VE: vaccine efficacy; IM: intramuscular; D: day

Study C4591001

Study C4591001 is an ongoing, randomized, placebo-controlled, observer-blind Phase 1/2/3 study being conducted in the U.S., Argentina, Brazil, Germany, South Africa and Turkey. Initially the study was designed as a Phase 1/2 study in healthy adults in the U.S. for vaccine candidate and dosage selection, as well as evaluation of immunogenicity and preliminary efficacy. The protocol was expanded to include a Phase 2/3 portion of the study to evaluate clinical disease efficacy endpoint in individuals 12 years of age and older in the U.S. and additional sites outside of the U.S.

The Phase 1 portion of the study was designed to identify a preferred vaccine candidate, vaccine dose, and administration schedule for further development based on the vaccine's safety, tolerability, and immunogenicity. To this end, two age groups were evaluated in separate cohorts, younger adults 18 through 55 years of age (N=45) and older adults 65 through 85 years of age (N=45). The study population included healthy men and women and excluded participants at high risk of SARS-CoV-2 infection or with serological evidence of prior or current SARS-CoV-2 infection. Two different vaccine candidates were evaluated, and younger participants received increasing dose levels (10, 20 and 30 µg) with progression to higher dose levels in a stepwise manner. Evaluation of increasing doses in the older age group (65 through 85 years) was based on recommendations from an internal review committee that reviewed safety and immunogenicity data derived from adults 18 through 55 years of age. For each vaccine candidate and dose, participants were randomized 4:1, such that 12 participants received the vaccine candidate and 3 participants received placebo. Review of the safety and immunogenicity from the Phase 1 portion of Study C4591001, in combination with data from Study BNT162-01, supported the final vaccine candidate, dose and dosing regimen (BNT162b2 administered at 30 µg, given 3 weeks apart) to proceed to the Phase 2/3 portion of Study C4591001.

In Phase 2/3, participants were enrolled with stratification by age (younger adults: 18 through 55 years of age; older adults: over 55 years of age) with the goal for the older age strata to consist of 40% of the entire study population. Adolescents were added to the protocol, based on review of safety data in younger adults enrolled in the ongoing study; thus, the age strata were revised as follows: 16 through 55 years of age, and 56 years of age and older. The study population for Phase 2/3 includes participants at higher risk for acquiring COVID-19 and at higher risk of severe COVID-19, such as participants working in the healthcare field, participants with autoimmune disease, and participants with chronic but stable medical conditions such as hypertension, asthma, diabetes, and infection with HIV, hepatitis B or hepatitis C. Participants were randomized 1:1 to receive 2 doses of either COMIRNATY or placebo, 3 weeks apart. The Phase 2 portion of the study evaluated reactogenicity and immunogenicity of the vaccine in 360

participants in the early stage of Phase 2/3, and these participants also contribute to the overall efficacy and safety data in the Phase 3 portion.

The ongoing Phase 3 portion of the study is evaluating the safety and efficacy of COMIRNATY for the prevention of COVID-19 occurring at least 7 days after the second dose of vaccine. Efficacy is being assessed throughout a participant's blinded follow-up in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness, an illness visit occurs. Assessments for illness visits include a nasal (mid-turbinate) swab, which is tested at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (i.e., Cepheid; FDA- authorized under EUA), or other sufficiently validated nucleic acid amplification-based test (NAAT), to detect SARS-CoV-2. The central laboratory NAAT result is used for the case definition, unless it was not possible to test the sample at the central laboratory. In that case, the following NAAT results are acceptable: Cepheid Xpert Xpress SARS-CoV-2, Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001), and Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001).

The study design included a planned interim analysis of the first primary efficacy endpoint (the efficacy of BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 in participants without evidence of SARS-CoV-2 infection before vaccination) at pre-specified numbers of COVID-19 cases (at least 62, 92, and 120 cases). All primary and secondary efficacy endpoints were analyzed in the final efficacy analysis after at least 164 COVID-19 cases were accrued. Participants are expected to participate for a maximum of approximately 26 months.

Per protocol, since December 14, 2020, following issuance of the emergency use authorization for the Pfizer-BioNTech COVID-19 Vaccine, study participants 16 years of age and older have been progressively unblinded to their treatment assignment (when eligible per local recommendations) and offered BNT162b2 vaccination if they were randomized to placebo.

The study was unblinded in stages as all ongoing participants were either individually unblinded (when eligible per local recommendations) or the subject had concluded their 6-month post–Dose 2 study visit. Participants 16 years of age and older who participated in the Phase 2/3 study were given the opportunity to receive COMIRNATY no later than the 6-month timepoint after the second study vaccination. Participants who originally received placebo but received COMIRNATY were moved to a new visit schedule to receive both doses of COMIRNATY, 3 weeks apart.

The primary safety and efficacy endpoints were:

1. Primary safety endpoint (descriptive): Solicited local adverse reactions (injection site pain, redness, swelling), solicited systemic adverse events (AE) (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain), unsolicited AEs, serious adverse events (SAEs).

2. First primary efficacy endpoint: COVID-19 incidence per 1000 person-years of follow-up based on laboratory-confirmed NAAT in participants with no serological or virological evidence (up to 7 days after Dose 2) of past SARS-CoV-2 infection.

3. Second primary efficacy endpoint: COVID-19 incidence per 1000 person-years of follow-up based on laboratory-confirmed NAAT in participants with and without serological or virological evidence (up to 7 days after Dose 2) of past SARS-CoV-2 infection.

The pertinent secondary endpoint was:

1. Severe COVID-19 incidence per 1000 person-years of follow-up.

Study C4591001 results

The population in the protocol-specified, event-driven final primary efficacy analysis included all participants 12 years of age and older who had been enrolled from July 27, 2020 and followed for the development of COVID-19 through November 14, 2020. For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0% (95% credible interval: 90.0, 97.9), which met the pre-specified success criterion. The case split was 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group. This protocol-specified, event-driven final primary efficacy analysis was the basis for issuance of the emergency use authorization for the Pfizer-BioNTech COVID-19 Vaccine on December 11, 2020.

Therefore, the primary study objective of VE against COVID-19 was met as the point estimate was above 50% and the lower bound of the 95% CI of the point estimate of VE was above 30%.

The population for the updated vaccine efficacy analysis per protocol included participants 16 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 during blinded placebo-controlled follow-up through March 13, 2021, representing up to ~6 months of follow-up after Dose 2. Overall, 60.8% of participants in the COMIRNATY group and 58.7% of participants in the placebo group had ≥4 months of follow-up time after Dose 2 in the blinded placebo-controlled follow-up period. The overall VE against COVID-19 in participants without evidence of prior SARS-CoV-2 infection was 91.1% (95% CI: 88.8 to 93.1). The overall VE against COVID-19 in participants with or without evidence of prior SARS-CoV-2 infection was 90.9% (95% CI: 88.5 to 92.8).

The updated vaccine efficacy information is presented in Tables 7a and 7b.

Table 7a: First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection - Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period *

Subgroup	COMIRNATY N[a]=19,993 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=20,118 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
All participants	77 6.092 (19,711)	833 5.857 (19,741)	91.1 (88.8, 93.1)
16 through 64 years	70 4.859 (15,519)	709 4.654 (15,515)	90.5 (87.9, 92.7)
65 years and older	7 1.233 (4192)	124 1.202 (4226)	94.5 (88.3, 97.8)

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Table 7b: First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection - Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period *

Subgroup	COMIRNATY N[a]=21,047 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,210 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
All participants	81 6.340 (20,533)	854 6.110 (20,595)	90.9 (88.5, 92.8)
16 through 64 years	74 5.073 (16,218)	726 4.879 (16,269)	90.2 (87.5, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Efficacy Against Severe COVID-19

Vaccine efficacy against severe COVID-19 for participants with or without prior SARS-CoV-2 infection is shown in Tables 8a and 8b. The VE against severe COVID-19 in participants with or without evidence of prior SARS-CoV-2 infection was 95.3% (95% CI: 71.0 to 99.9) using the protocol definition of severe COVID-19 and 100.0% (95% CI: 87.6 to 100.0) based on the CDC definition of severe COVID-19.

Table 8a: Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants 16 Years of Age and Older With or Without* Prior SARS-CoV-2 Infection Based on Protocol† Definition From 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up

	COMIRNATY Cases n1[a] Surveillance Time[b] (n2[c])	Placebo Cases n1[a] Surveillance Time[b] (n2[c])	Vaccine Efficacy % (95% CI[d])
7 days after Dose 2[d]	1 6.353 (20,540)	21 6.237 (20,629)	95.3 (70.9, 99.9)

Table 8b: Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants 16 Years of Age and Older With or Without* Prior SARS-CoV-2 Infection Based on Centers for Disease Control and Prevention (CDC)‡ Definition From 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up

	COMIRNATY Cases n1[a] Surveillance Time[b] (n2[c])	Placebo Cases n1[a] Surveillance Time[b] (n2[c])	Vaccine Efficacy % (95% CI[d])
7 days after Dose 2[d]	0 6.345 (20,513)	31 6.225 (20,593)	100 (87.6, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

† Severe illness from COVID-19 is defined in the protocol as confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of oxygen ≤93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300 mm Hg);
- Respiratory failure [defined as needing highflow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

‡ Severe illness from COVID-19 as defined by CDC is confirmed COVID-19 and presence of at least 1 of the following:

- Hospitalization;
- Admission to the Intensive Care Unit;
- Intubation or mechanical ventilation;
- Death.

a. n1 = Number of participants meeting the endpoint definition.
b. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
c. n2 = Number of participants at risk for the endpoint.

d. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time

Study BNT162-01

Study BNT162-01 is an ongoing Phase 1/2, open-label, dose-finding study to evaluate the safety and immunogenicity of several candidate vaccines, including BNT162b2 (1, 3, 10, 20, and 30 μg), conducted in Germany in healthy and immunocompromised adults. Only safety and immunogenicity data in individuals 16 years of age and older, the population for the intended use and who received the final vaccine formulation (30 µg BNT162b2) are used to support this application. The 30 µg dosage of BNT162b2 was administered to 12 adults 18 to 55 years of age and 12 adults 56 to 85 years of age.

The primary objective was to evaluate the safety of the BNT162 candidate vaccines. Secondary and exploratory objectives were to describe humoral and cellular immune responses following vaccination, measured at baseline and various time points after vaccination, specifically 7 days post Dose 2. Adverse event monitoring was the same as the safety monitoring in study C4591001.

The study started April 23, 2020. The BLA contains safety data (reactogenicity and AE analyses) up to 1 month after Dose 2 (data cutoff date: October 23, 2020), neutralizing antibody data up to ~2 months after Dose 2 (data cutoff date: October 23, 2020), and T-cell data up to ~6 months after Dose 2 (data cutoff date: March 2, 2021).

Study BNT162-01 Results

Disposition of 30 μg BNT162b2 group:

- Safety: Of a total of 24 participants, 12 participants 18 to 55 years of age and 12 participants 56 to 85 years of age completed the visit at 1- month post-Dose 2.
- Immunogenicity: Of the 12 participants, serum neutralizing antibody and T-cell responses were available for 10 and 12 participants, respectively.

Safety: The safety profiles for adult participants 18-55 and 56-85 years of age receiving 30 μg BNT162b2 in this study were similar to age-matched participants in study C4591001.

Immunogenicity: Dose-dependent increases were noted 42 days after Dose 2, compared to SARS-CoV-2 neutralizing GMTs at baseline (pre-Dose 1), and most pronounced at the 30 µg dose level. The Th1 polarization of the T-helper response was indicated by IFNγ and IL-2 production, and only minimal IL-4 production upon antigen-specific (SARS-CoV-2 S protein peptide pools) re-stimulation.

Review of the safety and immunogenicity from Phase 1 part of Study C4591001, in combination with data from Study BNT162-01, supported selection of the final vaccine candidate and dose level (BNT162b2 at 30 µg, given as two doses 3 weeks apart) to proceed into Phase 2/3 part of Study C4591001.

Lot Consistency

Consistency of process performance qualification (PPQ) batches manufactured at both Pfizer Puurs and Pfizer Kalamazoo was demonstrated by verifying process parameters and in-process testing results as well as DP release testing. Data obtained from the analytical comparability assessments on the PPQ batches manufactured at both sites

provide evidence of reproducible and consistent manufacture of COMIRNATY DP of acceptable product quality across all supply nodes.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance
BIMO inspection assignments were issued for a total of nine (9) clinical study sites that participated in the conduct of study Protocol C4591001. Three (3) of these inspection assignments focused on clinical study sites that enrolled the pediatric population and six (6) of the study sites enrolled the adult population. The inspections did not reveal findings that impact the BLA.

c. Pediatrics
The Applicant's Pediatric Plan was presented to the FDA Pediatric Review Committee (PeRC) on August 3, 2021. The committee agreed with the Applicant's request for a deferral for studies in participants 0 to <16 years of age because the biological product is ready for approval for use in individuals 16 years of age and older before pediatric studies in participants 0 to <16 years of age are completed (Section 505B(a)(3)(A)(i) of PREA).

The PREA-required studies specified in the approval letter and agreed upon with the Applicant are as follows:

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

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

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

7. Safety and Pharmacovigilance

The most commonly reported (≥10%) solicited adverse reactions in COMIRNATY recipients 16 through 55 years of age following any dose were pain at the injection site (88.6%), fatigue (70.1%), headache (64.9%), muscle pain (45.5%), chills (41.5%), joint pain (27.5%), fever (17.8%), and injection site swelling (10.6%). The most commonly reported (≥10%) solicited adverse reactions in COMIRNATY recipients 56 years of age and older following any dose were pain at the injection site (78.2%), fatigue (56.9%), headache, (45.9%), muscle pain (32.5%), chills (24.8%), joint pain (21.5%), injection site swelling (11.8%), fever (11.5%), and injection site redness (10.4%).

follow-up after Dose 2. There were no notable patterns between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to COMIRNATY.

From Dose 1 through the March 13, 2021 data cutoff date, there were a total of 38 deaths, 21 in the COMIRNATY group and 17 in the placebo group. None of the deaths were considered related to vaccination.

Since the issuance of the EUA (December 11, 2020), post-authorization safety data has been reported from individuals 16 years of age and older following any dose of COMIRNATY. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Below are presented adverse reactions categorized as important identified risks in the pharmacovigilance plan that have occurred during the conduct of the clinical trial and have been reported following the issuance of the EUA.

Myocarditis/Pericarditis

During the time from Dose 1 to unblinding in Study C4591001, one report of pericarditis was identified in the COMIRNATY group, occurring in a male participant ≥55 years of age, with no medical history, 28 days after Dose 2; the event was assessed by the investigator as not related to the study intervention and was ongoing at the time of the data cutoff. One report of myocarditis was identified in a male participant <55 years of age in the placebo group, occurring 5 days after his second placebo dose.

Post-EUA safety surveillance reports received by FDA and CDC identified serious risks for myocarditis and pericarditis following administration of COMIRNATY. Reporting rates for medical chart-confirmed myocarditis/pericarditis in VAERS have been higher among males under 40 years of age than among females and older males and have been highest in males 12-17 years of age (65 cases per million doses administered as per CDC communication on August 20, 2021), particularly following the second dose, and onset of symptoms within 7 days following vaccination. Although some cases of vaccine-associated myocarditis/pericarditis required intensive care support, available data from short-term follow up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae and outcomes in affected individuals. A mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established.

These safety findings of increased risk for myocarditis/pericarditis led to warning in section 5.2 Warning and Precautions of the PI.

Myocarditis and pericarditis are considered important identified risks in the pharmacovigilance plan included in the BLA. Of note, the Applicant will be required to conduct postmarketing requirement (PMR) safety studies under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the known serious risks of myocarditis and pericarditis as well as an unexpected serious risk for subclinical myocarditis (see Section 11c Recommendation for Postmarketing Activities, for study details).

Moreover, since vaccine-associated myocarditis/pericarditis is the most clinically significant identified risk, FDA undertook a quantitative benefit-risk assessment to model the excess risk of myocarditis/pericarditis vs. the expected benefits of preventing COVID-19 and associated hospitalizations, ICU admissions, and deaths. For estimation of risk, the model took a conservative approach by relying on non-chart-confirmed cases from a US healthcare claims database (OPTUM) that could provide a control group and greater confidence in denominators for vaccine exposures. Thus, the estimates of excess risk in this model are higher than the rates estimated from reports to VAERS (an uncontrolled passive surveillance system), with an estimated excess risk approaching 200 cases per million vaccinated males 16-17 years of age (the age/sex-stratified group with the highest risk). For estimation of benefit, the model output was highly dependent on the assumed COVID-19 incidence, as well as assumptions about vaccine efficacy and duration of protection. The assessment therefore considered a range of scenarios including but not limited to a “most likely” scenario associated with recent Delta variant surge and diminished vaccine effectiveness (70% overall, 80% against COVID-19 hospitalization) compared to that observed in the clinical trial. The “worst-case” scenario with low COVID-19 incidence reflecting the July 2021 nadir and the same somewhat diminished vaccine effectiveness as in the “most likely” scenario.

For males and females 18 years of age and older and for females 16-17 years of age, even before accounting for morbidity prevented from non-hospitalized COVID-19, the model predicts that the benefits of prevented COVID-19 hospitalizations, ICU admissions and deaths would clearly outweigh the predicted excess risk of vaccine-associated myocarditis/pericarditis under all conditions examined. For males 16-17 years of age, the model predicts that the benefits of prevented COVID-19 hospitalizations, ICU admissions and deaths would clearly outweigh the predicted excess risk of vaccine-associated myocarditis/pericarditis under the “most likely” scenario, but that predicted excess cases of vaccine-associated myocarditis/pericarditis would exceed COVID-19 hospitalizations and deaths under the “worst case” scenario. However, this predicted numerical imbalance does not account for the greater severity and length of hospitalization, on average, for COVID-19 compared with vaccine-associated myocarditis/pericarditis. Additionally, the “worst case” scenario model predicts prevention of >13,000 cases of non-hospitalized COVID-19 per million vaccinated males 16-17 years of age, which would include prevention of clinically significant morbidity and/or long-term sequelae associated with some of these cases. Finally, the model does not account for indirect societal/public health benefits of vaccination. Considering these additional factors, FDA concluded that even under the “worst case” scenario the benefits of vaccination sufficiently outweigh risks to support approval of the vaccine in males 16-17 years of age.

Mitigation of the observed risks and associated uncertainties will be accomplished through labeling (including warning statements) and through continued safety surveillance and postmarketing studies to further assess and understand these risks, including an immunogenicity and safety study of lower dose levels of COMIRNATY in individuals 12 through <30 years of age. The Applicant will be required to conduct postmarketing requirement (PMR) safety studies under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the known serious risks of myocarditis and pericarditis and an unexpected serious risk for subclinical myocarditis (see section 11c for study details).

Anaphylaxis
The risk of anaphylaxis was recognized early in the post-authorization time period and it is included as an important identified risk in the PVP. The estimated crude reporting rate for anaphylaxis is 6.0 cases per million doses. Therefore, the incidence of anaphylaxis after receipt of COMIRNATY is comparable with those reported after receipt of other vaccines.

There were no reports of anaphylaxis associated with COMIRNATY in clinical study participants through the cutoff date of March 13, 2021.

A contraindication for individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of COMIRNATY is included in section 4 of the PI. Additionally, a warning statement is included in section 5.1 of the PI instructing that "appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of COMIRNATY"

Pharmacovigilance Plan (PVP)
The Applicant's proposed pharmacovigilance plan (version 1.1) includes the following important risks and missing information:

- Important identified risks: Anaphylaxis; Myocarditis and Pericarditis
- Important potential risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
- Missing information: Use in pregnancy and lactation; Vaccine effectiveness; Use in pediatric individuals <12 years of age

In addition to routine pharmacovigilance, the Applicant will conduct the postmarketing studies listed in Section 11c Recommendation for Postmarketing Activities.

Adverse event reporting under 21 CFR 600.80 and the postmarketing studies in Section 11c are adequate to monitor the postmarketing safety for COMIRNATY.

8. Labeling

The proprietary name, COMIRNATY, was reviewed by CBER's Advertising and Promotional Labeling Branch (APLB) on July 2, 2021, and found to be acceptable. CBER communicated this decision to the Applicant on July 6, 2021. The APLB found the PI and package/container labels to be acceptable from a promotional and comprehension perspective. The Review Committee negotiated revisions to the PI, including modifying the proposed proper name from "COVID-19 mRNA vaccine (nucleoside-modified)" to "COVID-19 Vaccine, mRNA" and including a warning for an increased risk of myocarditis and pericarditis following administration of COMIRNATY. All labeling issues regarding the PI and the carton and container labels were acceptably resolved after exchange of information and discussions with the Applicant.

9. Advisory Committee Meetings

Vaccines and Related Biological Products Committee (VRBPAC) meetings were convened on October 22, 2020 to discuss, in general, development for EUA and licensure of vaccines to prevent COVID-19 and on December 10, 2020, to discuss BioNTech Manufacturing GmbH/Pfizer's EUA request for the Pfizer-BioNTech COVID-19 Vaccine.

On October 22, 2020, the VRBPAC was presented with the following items for discussion (no vote):

1. Please discuss FDA's approach to safety and effectiveness data as outlined in the respective guidance documents.

2. Please discuss considerations for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine.

3. Please discuss studies following licensure and/or issuance of an EUA for COVID-19 vaccines to
    a. Further evaluate safety, effectiveness and immune markers of protection
    b. Evaluate the safety and effectiveness in specific populations

In general, the VRBPAC endorsed FDA's approach and recommendations on the safety and effectiveness data necessary to support a BLA and EUA for COVID-19 vaccines as outlined in the respective guidance documents. VRBPAC members recommended for the median follow-up of 2 month to be the minimum follow-up period and suggested longer follow-up periods to evaluate, both safety and efficacy, if feasible. The VRBPAC endorsed the importance of additional studies to further evaluate safety and effectiveness of the vaccine after EUA issuance and/or licensure and underscored the need to evaluate the safety and effectiveness of COVID-19 vaccines in specific populations.

On December 10, 2020, VRBPAC discussed Pfizer- BioNTech Manufacturing GmbH's EUA request for their vaccine to prevent COVID-19 in individuals 16 years of age and older. The committee discussed the safety and efficacy data derived from the clinical disease endpoint efficacy study C4591001.

The VRPBAC voted on one question:

1. Based on the totality of scientific evidence available, do the benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its risks for use in individuals 16 years of age and older?

    The results of the vote were as follows:
    Yes = 17 No = 4 Abstain = 1

The VRBPAC was presented with the following items for discussion (no vote):

1. Pfizer has proposed a plan for continuation of blinded, placebo-controlled follow-up in ongoing trials if the vaccine were made available under EUA. Please discuss

Pfizer's plan, including how loss of blinded, placebo-controlled follow-up in ongoing trials should be addressed.

2. Please discuss any gaps in plans described today and in the briefing documents for further evaluation of vaccine safety and effectiveness in populations who receive the Pfizer-BioNTech COVID-19 Vaccine under an EUA.

The committee discussed potential implications of loss of blinded, placebo-controlled follow-up in ongoing trials including how this may impact availability of safety data to support a BLA. The VRBPAC commented on the need to further assess vaccine effect on asymptomatic infection and viral shedding, and further evaluation of safety and effectiveness in subpopulations such as HIV-infected individuals, individuals with prior exposure to SARS-CoV-2.

FDA did not refer this application to the VRBPAC because our review of the information submitted to this BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

a. Identification of BLA Lots

Upon CBER's request inquiring about what BLA-compliant EUA-labeled lots may be available for use upon licensure of COMIRNATY, the Applicant submitted information listing which lots they considered to be manufactured according to the BLA. To address the issue of these lots not bearing the vial label associated with BLA approval, CBER worked with the Applicant to develop a Dear HCP letter to be included with lots considered by CBER to be BLA-compliant. This letter explained that some lots labeled for EUA use were also considered BLA-compliant and refers HCP to a website for additional information. CBER requested and the Applicant agreed that only EUA-labeled lots that had also undergone CBER lot release according to the BLA would be considered BLA-compliant and listed at the website included in the Dear HCP letter.

b. Exception to the 21 CFR 610.15(a) Requirement for a Preservative

Under 21 CFR 610.15(a), a vaccine product in multiple-dose containers must (absent certain exceptions) contain a preservative. The Applicant submitted a request for exception to this requirement and provided a justification for the multi-dose presentation of COMIRNATY not containing a preservative. CBER considered the Applicant's request for an exception to the 21 CFR 610.15(a) for COMIRNATY as a multiple dose preservative-free presentation acceptable.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on the review of the clinical, pre-clinical, and product-related data submitted in the original BLA, the Review Committee recommends approval of COMIRNATY for the labeled indication and usage.

b. Benefit/Risk Assessment

Considering the data submitted to support the safety and effectiveness of COMIRNATY that have been presented and discussed in this document, as well as the seriousness of COVID-19, the Review Committee is in agreement that the risk/benefit balance for COMIRNATY is favorable and supports approval for use in individuals 16 years of age and older.

c. Recommendation for Postmarketing Activities

BioNTech Manufacturing GmbH has committed to conduct the following postmarketing activities, which will be included in the approval letter.

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

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

   Final Protocol Submission: August 31, 2021
   Monitoring Report Submission: October 31, 2022
   Interim Report Submission: October 31, 2023
   Study Completion: June 30, 2025
   Final Report Submission: October 31, 2025

2. Study C4591021, entitled "Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY

   Final Protocol Submission: August 11, 2021
   Progress Report Submission: September 30, 2021
   Interim Report 1 Submission: March 31, 2022
   Interim Report 2 Submission: September 30, 2022
   Interim Report 3 Submission: March 31, 2023
   Interim Report 4 Submission: September 30, 2023
   Interim Report 5 Submission: March 31, 2024
   Study Completion: March 31, 2024
   Final Report Submission: September 30, 2024

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

   Final Protocol Submission: January 31, 2022
   Study Completion: March 31, 2024
   Final Report Submission: September 30, 2024

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

Final Protocol Submission: November 30, 2021
Study Completion: December 31, 2026
Final Report Submission: May 31, 2027

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

   Final Protocol Submission: September 30, 2021
   Study Completion: November 30, 2023
   Final Report Submission: May 31, 2024

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

   Final Protocol Submission: November 30, 2021
   Study Completion: June 30, 2022
   Final Report Submission: December 31, 2022

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

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

   Final Protocol Submission: July 1, 2021
   Study Completion: June 1, 2025
   Final Report Submission: December 1, 2025

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

   Final Protocol Submission: September 30, 2021
   Study Completion: November 30, 2023
   Final Report Submission: May 31, 2024

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

   Final Protocol Submission: January 29, 2021
   Study Completion: June 30, 2023
   Final Report Submission: December 31, 2023

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

Final Protocol Submission: March 22, 2021
Study Completion: December 31, 2022
Final Report Submission: June 30, 2023

PEDIATRIC REQUIREMENTS

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

    Final Protocol Submission: October 7, 2020
    Study Completion: May 31, 2023
    Final Report Submission: October 31, 2023

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

    Final Protocol Submission: February 8, 2021
    Study Completion: November 30, 2023
    Final Report Submission: May 31, 2024

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

    Final Protocol Submission: January 31, 2022
    Study Completion: July 31, 2024
    Final Report Submission: October 31, 2024

Exhibit N

Southwest Airlines cancels 1,800 flights days after pilot union sued over Covid-19 vaccine mandate

Company blamed problems on 'disruptive weather' and air traffic control issues

Graeme Massie Los Angeles | Monday 11 | comments

Southwest Airlines cancels thousands of flights

Southwest Airlines cancelled at least 1,800 flights just days after its pilot union sued the company over its Covid-19 vaccine mandate.

Southwest was forced to cancel more than 1,000 flights on Sunday, around 30 per cent of its US schedule, according to the FlightAware website.

And it blamed "disruptive weather" and air traffic control issues for its problems.

But the Federal Aviation Administration said that airlines were experiencing problems because of their own difficulties with staffing and aircraft

aircraft.

And another 800 flights were cancelled on Saturday, according to The Washington Post.

The airline said in a Sunday statement that its problems began on Friday because of weather issues at its Florida airports that "were compounded by unexpected air traffic control issues in the same region, triggering delays and prompting significant cancellations for us beginning Friday evening."

Southwest's issues with weather and traffic control did not appear to be shared by other airlines.

American Airlines reportedly had around 63 cancellations as of early Sunday afternoon and United Airlines only had nine.

The FAA responded by saying that there were some air traffic staffing issues but that the main issue belonged to the airlines.

"Flight delays and cancellations occurred for a few hours Friday afternoon due to widespread severe weather, military training, and limited staffing in one area of the Jacksonville Air Route Traffic Control Center," the FAA said in a Sunday statement.

"Some airlines continue to experience scheduling challenges due to aircraft and crews being out of place."

Southwest said it was attempting to reposition aircraft and crews so that service could get back to normal.

The Southwest Airlines Pilots Association said in its own statement that pilots that although it was aware of "operational difficulties affecting Southwest Airlines" it could "say with confidence that our Pilots are not participating in any official or unofficial job actions."

And the union added: "Our Pilots will continue to overcome (Southwest) management's poor planning, as well as any external operational challenges, and remain the most productive Pilots in the world."

Recommended

Your biggest questions about the death penalty answered by legal experts

Interpreter who helped rescue Joe Biden finally escapes Afghanistan

Elon Musk trolls Jeff Bezos as he falls further behind in 'world's richest' race

The Southwest Airlines Pilots Association, which on Tuesday said it was filing a temporary restraining order against the Dallas airline related to its

Most popular

PS5 stock UK - live: Today's restock updates from Game, Argos and more

Warner Bros releases strong statement after Ruby Rose alleges abuse

Brian Laundrie update: Human remains and notebook found

Squid Game VIP actors react to criticism of their acting

Popular videos

Crowd chants 'justice for Gabby' during FBI conference after human remains found

Mary Berry 'very thrilled' to be honoured with damehood

Couple float 100-year-old dream house to new location across bay in Canada

indy100 TRENDING

Pub landlord shames customers who ate meal but refused to pay

Bartender quits after boss 'says he can't get drunk on day off'

Professor calls out GMB as male counterpart given title but she's not

Police investigating after TV news station accidentally airs

filing a temporary restraining order against the Dallas airline related to its August lawsuit over Covid-19 mandates.

Southwest says all of its employees must be vaccinated against Covid-19 by 8 December or face losing their job.

news station accidentally airs porn

'You haven't got a clue': Farage scolded on Irish TV over IRA video

Exhibit O

Southwest Airlines debacle is symptomatic of bigger pandemic problems

BY SHELDON H. JACOBSON, PH.D., OPINION CONTRIBUTOR — 10/18/21 05:00 PM EDT
THE VIEWS EXPRESSED BY CONTRIBUTORS ARE THEIR OWN AND NOT THE VIEW OF THE HILL

273 COMMENTS

42 SHARES

SHARE TWEET

© Greg Nash

Southwest Airlines had more than 2,000 flight cancellations last week. There is nothing to indicate that such cancellations will permanently stop, and they may even bleed into the upcoming busy travel holiday season, with travelers across the nation inconvenienced.

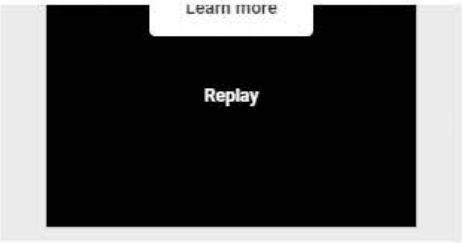
Southwest management attributed the onslaught of flight cancellations to air traffic control issues and weather problems. Although these factors may have contributed to such cancellations, they are unlikely to have been the primary cause, since no other airlines experienced such widespread flight disruptions during the same period.

The key driver for such cancellations is likely the COVID-19 vaccine mandate for its employees. Southwest employees are expressing their concern in droves by simultaneously and strategically using their sick time benefits.

AdChoices

Ad removed. Details

Southwest has built a reputation on taking care of its employees, which has resulted in unprecedented profitability during the most challenging economic downturns, a



record that none of the other legacy airlines like American, Delta and United have been able to match.

Some employees believe that the vaccine mandate is in direct contradiction to Southwest's internal practice of "employees first, customers second." If Southwest adhered to this policy, employees may think that the company would find a workable solution to meet their wishes. Clearly, some employees believe that not showing up for work is preferable to being subject to a top-down federal mandate that they believe is not in their best interests.

There are several factors that make Southwest particularly vulnerable to widespread employee no-shows.

Southwest does not employ a hub-and-spoke system like the other legacy airlines. That means their schedule is designed around point-to-point flights. As such, there are fewer flight alternatives with flight cancellations for any reason. It also makes it more difficult to fill pilot and flight attendant requirements when such people call in sick or become unavailable on short notice. This makes Southwest more vulnerable to staffing shortages than the other legacy airlines, who can move pilots and flight attendants around with greater ease and facility.

Given that Southwest has around 55,000 employees, if each flight cancelled involved just two employees scheduled to cover three flights, then that translates into just over 2 percent of their employees being unavailable. This illustrate how vulnerable the airline is to organized worker shortages even among a small group of potentially disgruntled employees.

ADVERTISING

Southwest falls under President Biden's vaccination mandate, so they must abide by it: requiring that employees for companies with more than 100 workers get vaccinated. Although some employees under this mandate can opt for weekly COVID-19 testing in lieu of vaccination, federal contractors — like airlines — cannot.

Most Popular

1 Trump announces new social media...
220 SHARES

2 Manchin on party switch: 'It's...
151 SHARES

3 The Memo: Cuts to big bill vex...
80 SHARES

4 Meghan McCain: 'SNL' parodies made...
62 SHARES

5 Regional powers rally behind...
60 SHARES

6 Sailors didn't know what to do in...
56 SHARES

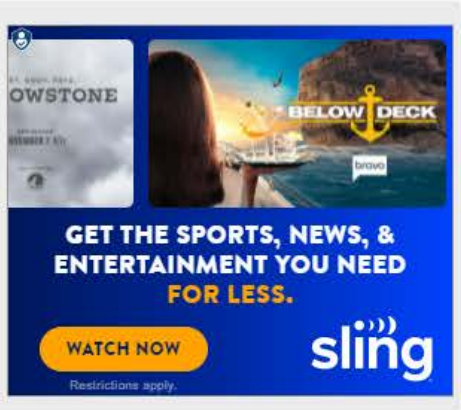
LOAD MORE

Texas Gov. Greg Abbot (R) issued a ban to stop the implementation of vaccine mandates. The Southwest Pilot Union is also fighting any mandates for their members. However, both Southwest and American Airlines, which are both based out of Dallas will continue to require all their employees to abide by the federal vaccine mandate.

Southwest employees not showing up for work is effectively a strike. Using sick time benefits means that employees can be paid while coordinating their efforts to send a message about vaccination. Such a systematic process can be used periodically to communicate their displeasure with any company policy, including the current vaccine mandate.

Southwest's company policy seemingly does everything to keep its employees happy. When confronted with a federal mandate that a minority of (but vociferous) employees is unhappy with, it became vulnerable to flight disruptions and cancellations that other airlines could better buffer.

The lesson learned from this is that a company is only as strong as its people, and when some of them revolt, there are consequences.



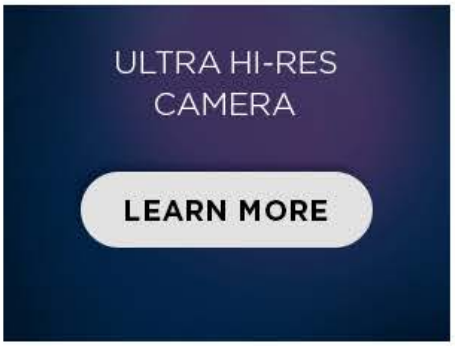
New York City launching ad blitz to lure back foreign tourists

UK secures deals with Merck, Pfizer for COVID-19 antiviral pills

The biggest loser in this ordeal are the customers who became innocent victims of the actions of a few. Given the alternatives available in the vaccine mandate, these employees may wish to rethink their strategy moving forward. If a sufficient number of customers ditch Southwest for seemingly more reliable competitors, they may find themselves without a job to call in sick to. Then they will get their wish and no longer require vaccination.

Sheldon H. Jacobson, Ph.D., is a founder professor of Computer Science at the University of Illinois at Urbana-Champaign. He applies his expertise in data-driven risk-based decision-making to evaluate and inform public health policy. His research provided the technical foundations for TSA PreCheck.

This piece has been updated to reflect vaccination mandates for federal contractors.



Video

Health expert says other COVID-19 variants 'pale in comparison' to delta

RISING

Meet the company that is revolutionizing e-commerce by conquering the mountain of packages outside your front door

CHANGING AMERICA

Policy analyst says massive defense bill puts US in 'arms race' with China

RISING

Exhibit P

Southwest CEO says he's against vaccine mandates, blames Biden

By Emily Crane

October 12, 2021 | 12:45pm | Updated

MORE ON:
SOUTHWEST AIRLINES

Southwest nixes plan to put these unvaccinated staff on unpaid leave

DOT to audit staffing challenges after Southwest Airlines chaos

High-rolling hound: Couple shocked to find Chihuahua hiding in luggage moments before flight to Vegas

Analysts skeptical of Southwest's explanation on mass cancelations

Southwest Airlines CEO Gary Kelly says he's against making his employees take the COVID-19 vaccine, but President Biden has forced his hand with the federal mandate.

"I've never been in favor of corporations imposing that kind of a mandate. I'm not in favor of that, never have been," Kelly told CNBC's "Squawk on the Street" on Tuesday regarding the COVID-19 vaccine.

Kelly said his employees "have very strong views on both sides" of the issue of vaccine mandates but they were being forced to take it given Biden's executive order.

"The executive order from President Biden mandates that all federal employees and then all federal contractors, which covers all the major airlines, have to have a mandate vaccine in place by Dec. 8 so we're working through that," Kelly said.

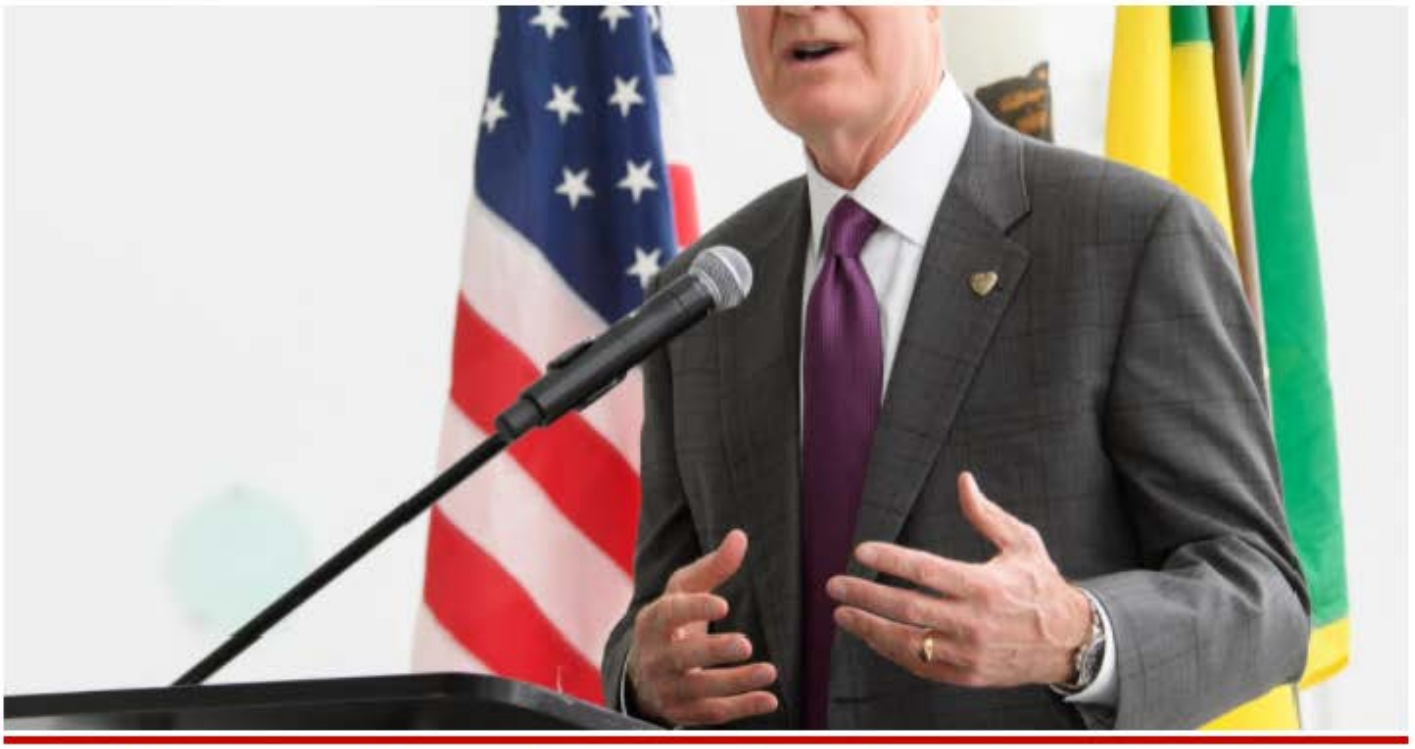
The CEO said Southwest is urging all employees to get vaccinated because his goal is to make sure none of his employees lose their jobs.

"If they can't (get vaccinated), we're urging them to seek an accommodation either for medical or religious reasons," Kelly said. "The objective here, obviously, is to improve health and safety, not for people to lose their jobs."

Gary Kelly says Southwest was forced to implement the vaccine mandate given President Biden's executive order.
Olivier Douliery/AFP via Getty Images

Southwest is offering employees the equivalent of two days' pay as an incentive to get vaccinated, and to compensate them for any potential side effects, Kelly said.

It comes after the airline was rocked by mass cancellations that forced Southwest to ground more than 25 percent of its scheduled flights over the weekend and another 10 percent on Monday.



Southwest Airlines CEO Gary Kelly came out against COVID-19 vaccination mandates, saying, "I'm not in favor of that, never have been."

Patrick T. Fallon/AFP via Getty Images

Kelly and the Federal Aviation Administration have both said the vaccine mandate was not to blame for the recent travel chaos.

Southwest is offering employees the equivalent of two days' pay as an incentive to get vaccinated.
Steven Senne/AP

"To be clear: None of the information from Southwest, its pilots union, or the FAA indicates that this weekend's cancellations were related to vaccine mandates," the FAA tweeted Monday evening.

Kelly echoed the FAA in an interview with ABC's "Good Morning America" Tuesday morning, saying "there's just no evidence of that."

"I want to apologize to all of our customers. This is not what we want but unfortunately it just takes a couple of days to get things back on track," he added.

Gary Kelly echoed the FAA in assuring that the mass Southwest flight cancellations were not tied to the vaccine mandate.
Jim Lo Scalzo/EPA-EFE/Shutterstock

As of 9 a.m. ET Tuesday, Southwest had canceled about 90 scheduled flights, or about 2 percent of the day's departures, according to Flight Aware. Another nearly 250 were delayed, the site said.

Additional reporting by Will Feuer

Exhibit Q

Southwest drops plan to put unvaccinated staff on unpaid leave starting in December

PUBLISHED TUE, OCT 19 2021•9:10 AM EDT | UPDATED TUE, OCT 19 2021•8:08 PM EDT

Leslie Josephs
@LESLIEJOSEPHS

SHARE

KEY POINTS

- Southwest scrapped a plan to put unvaccinated workers with pending exemptions on unpaid leave after the Dec. 8 deadline.
- Both American and Southwest require their new-hire employees to show proof of Covid-19 vaccination before their first day.
- Large airlines are federal contractors and subject to a Biden administration order that requires their employees to be vaccinated or receive an exemption for medical or religious reasons.

Travelers wait to check in at the Southwest Airlines ticketing counter at Baltimore Washington International Thurgood Marshall Airport on October 11, 2021 in Baltimore, Maryland.
Kevin Dietsch | Getty Images

Southwest Airlines has scrapped a plan to put unvaccinated employees who

CNBC TV
Worldwic
Exchange
UP NEXT | Squa

TRENDING

1
2
3
4

have applied for but haven't received a religious or medical exemption on unpaid leave as of a federal deadline in December.

Southwest Airlines and American Airlines are among the carriers that are federal contractors and subject to a Biden administration requirement that their employees are vaccinated against Covid-19 by Dec. 8 unless they are exempt for medical or religious reasons.

Rules for federal contractors are stricter than those expected from the Biden administration for large companies, which will allow for regular Covid testing as an alternative to a vaccination.

Executives at both carriers in recent days have tried to reassure employees about job security under the mandate, urging them to apply for exemptions if they can't get vaccinated for a medical reason or for a sincerely held religious belief. The airlines are expected to face more questions about the mandate when they report quarterly results Thursday morning. Pilots' labor unions have sought to block the mandates or sought alternatives such as regular testing.

Southwest's senior vice president of operations and hospitality, Steve Goldberg, and Julie Weber, vice president and chief people officer, wrote to staff on Friday that if employees' requests for an exemption haven't been approved by Dec. 8, they could continue to work while following mask and distancing guidelines until the request has been reviewed.

The company is giving employees until Nov. 24 to finish their vaccinations or

FROM THE W

Galaxy Book
to PC
Samsung

Save more w
Percentage
Citi® Online Savin

apply for an exemption. It will continue paying them while the company reviews their requests and said it will allow those who are rejected to continue working "as we coordinate with them on meeting the requirements (vaccine or valid accommodation)."

"This is a change from what was previously communicated. Initially, we communicated that these Employees would be put on unpaid leave and that is no longer the case," they wrote in the note, which was reviewed by CNBC.

Southwest confirmed the policy change, which comes just weeks before the deadline.

United Airlines implemented its own vaccine mandate in August, a month before the government rules were announced. United had told staff that they would be put on unpaid leave if they received exemptions. More than 96% of its staff is vaccinated. Some employees sued the company over the unpaid leave, and a federal judge in Fort Worth, Texas, has temporarily blocked the airline from going forward with its plan.

American's CEO, Doug Parker, spoke with labor union leaders on Thursday to discuss vaccine exemptions.

American Airlines management "indicated that, unlike the approach taken by United, they were exploring accommodations that would allow employees to continue to work," the Association of Professional Flight Attendants, the union that represents American's mainline cabin crews, said in a note to members Monday. "They failed to offer any specifics as to what such accommodations might look like at that time."

The Fort Worth, Texas-based airline confirmed to employees Tuesday that they can continue to work if they are granted an exemption or if their exemption requests are still being reviewed. Those workers could have to follow certain protocols, like wearing a mask and providing regular health declarations, however.

American also told staff to apply for exemptions as soon as possible, writing in an internal staff post about the mandate that the "process to review all requests will take time, as we want to ensure we give full consideration to all requests."

Choosing not to be vaccinated and not receiving an exemption may still result in termination, American said. It is not planning voluntary leaves or early retirement packages for those who choose not to get vaccinated.

"We want all of our team members to be vaccinated so they can continue working at American," it said. "We need our entire team to run the airline in 2022 and beyond and are not looking to reduce headcount."

The Allied Pilots Association, which represents American's roughly 14,000 pilots, wrote to the White House and several key lawmakers on Sept. 24, urging an alternative to the mandate such as regular testing, warning the mandate "could result in labor shortages and create serious operational problems for American Airlines and its peers."

Hundreds of Southwest employees, customers and other protesters demonstrated Monday against the vaccine mandate outside Southwest Airlines' headquarters in Dallas, The Dallas Morning News reported.

An airline spokeswoman said the carrier is aware of the demonstration.

"Southwest acknowledges various viewpoints regarding the Covid-19 vaccine, and we have always supported, and will continue to support, our employees' right to express themselves, with open lines of communication to share issues and concerns," she said.

Southwest's Goldberg and Weber told staff that if an employee's request for exemption is denied, the employee can reapply if the employee "has new information or circumstances it would like the Company to consider."

Southwest requires new-hire employees to be vaccinated, as does American Airlines for new staff for its mainline operation, spokesmen said.

Delta Air Lines is also a federal contractor subject to the government requirements, but it hasn't yet required staff vaccinations. Last week, the carrier reported that about 90% of its roughly 80,000 employees are vaccinated. In August, Delta announced unvaccinated staff would start paying $200 more a month for company health insurance in November.

Exhibit R

Biden's vaccine mandate is making America's most serious economic problem worse

BY LIZ PEEK, OPINION CONTRIBUTOR — 09/29/21 09:00 AM EDT
THE VIEWS EXPRESSED BY CONTRIBUTORS ARE THEIR OWN AND NOT THE VIEW OF THE HILL

907 COMI

523 SHARES

SHARE TWEET

© Getty Images

We have exactly one serious economic problem in this country today: not enough Americans are working. President Biden's vaccine mandate is making the problem worse.

A shortage of labor is disrupting supply chains and boosting inflation, which is eating into middle class paychecks and undermining seniors' retirement. Rising prices are one reason consumer confidence has dropped over the past three months; if the slump persists, it will ultimately dampen spending.

Another factor hindering our recovery is that there are too few workers. It's crimping business revenues and small firm optimism. If restaurants and stores can't hire staff, they miss out on orders and have to shorten their hours. This is happening all over the country.

AdChoices

This is where Biden should be laser focused. Not on spending trillions of dollars on lavish Democratic priorities such as universal pre-

upwork

Hire in-demand data analysts

Most Popular

1 Trump announces nev social media...

220 SHARES

2 Manchin on party swi 'It's...

Learn more

priorities such as universal pre-kindergarten and expanding Medicare but on helping alleviate the worker shortage and related supply bottlenecks.

Instead, he is making them worse by directing the Occupational Safety and Health Administration (OSHA) to issue a new temporary emergency standard to mandate COVID-19 vaccination or regular testing for companies with more than 100 employees.

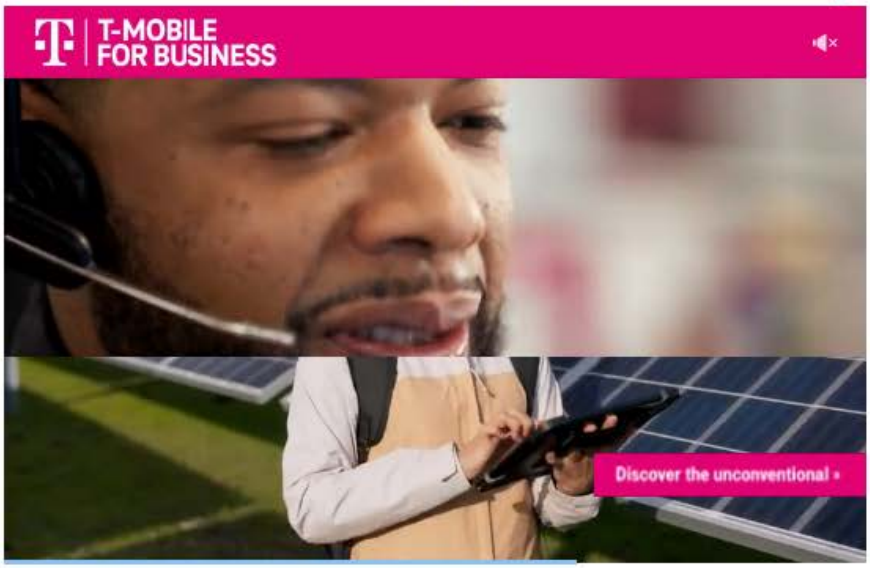
That vaccine mandate is driving people out of the workforce, rather than encouraging them to come back in. This trend is especially concerning as it is benching all-important health care workers.

New York's largest hospital system, Northwell Health, recently fired two dozen managers because they refused the jab. Thousands more could follow; CBS News reports some "16% of the state's hospital workers are not fully vaccinated, which means more than 83,000 are at risk of termination."

The state is considering calling in the National Guard to replace hospital workers who have been fired. Somehow, that doesn't seem optimal for patients. In North Carolina, similarly, a hospital system has fired some 175 employees for not taking the shot, in what the Washington Post called "one of the largest-ever mass terminations due to a vaccine mandate."

Imagine: In the midst of a pandemic, we are losing health care workers.

ADVERTISING



This is just the beginning. Airline pilots, school teachers, Big Tech workers and employees in many other sectors face being fired unless they get the shots. United Airlines just announced it is set to fire nearly 600 workers who are refusing to be vaccinated.

Companies that are struggling mightily to hire workers, such as Amazon

151 SHARES

3 The Memo: Cuts to big vex...
80 SHARES

4 Meghan McCain: 'SNL parodies made...
62 SHARES

5 Regional powers rally behind...
60 SHARES

6 Sailors didn't know wl to do in...
56 SHARES

LOAD MORE

Video

Health expert says other COV 19 variants 'pale in comparisc delta

RISING

Companies that are struggling mightily to hire workers, such as Amazon and FedEx, are wary of complying with Biden's demand, knowing they will have a hard time replacing anyone they let go. While these businesses and others have re-imposed mask mandates, they are not about to further thin their ranks by demanding everyone get the vaccine.

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

But it is also because of a shortage of workers.

Experts fear that Biden's new mandate will worsen delays at the ports and elsewhere. Jeremy Tancredi, a partner in a consulting firm specializing in supply chain management, told a publication focused on sourcing issues the mandate could have "an undesirable impact" as some unvaccinated workers push back and look for opportunities at companies that are not subject to the same requirements.

Another expert in the field was quoted as saying, "Supply Chains are struggling – high costs, scarce capacity and raw materials, etc. – and the mandate is another constraint to be managed."

It's not just firms involved in warehousing and ports that could be further disrupted by the vaccine mandate. Truckers, who already face a serious labor shortage, could also be impacted. The CEO of American Trucking Associations put out a statement saying:

"ATA, its members and our drivers remain committed to delivering life-saving COVID vaccines, but these proposed requirements—however well-intentioned—threaten to cause further disruptions throughout the supply chain, impeding our nation's COVID response efforts and putting the brakes on any economic revival."

President Biden may think that imposing vaccine mandates will hasten the end of the pandemic. He could be right; certainly the requirement polls well for just that reason. But such requirements are leading to even fewer workers on the job, and that is a problem. Especially when it effects the number of health care workers.

It is not the only White House directive that is keeping people at home, of course.

It has been well documented that the extended unemployment benefits included in the Democrats' $1.9 trillion American Rescue Plan encouraged folks to stay home. One study reported that "in all 25 states that are continuing the UI bonus, a family of four can currently receive the annual

Meet the company that is revolutionizing e-commerce conquering the mountain of packages outside your front

CHANGING AMERICA

Policy analyst says massive defense bill puts US in 'arms with China

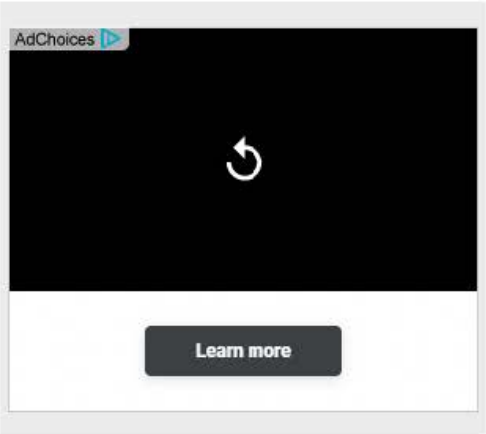
RISING

How one restaurateur is feedi the hungry and helping restaurants stay open during pandemic

CHANGING AMERICA

equivalent of more than $82,000 in income—while not working. In 19 states and D.C., the amount is more than $100,000."

People are rational. If you can receive the equivalent of our country's median income while sitting on the sofa, you will probably sit on the sofa.



Those unemployment payments have, thankfully, expired, despite Democrats' best efforts to keep them rolling. But Biden's rent moratorium, child tax credits (in the form of generous monthly checks), widespread student loan cancellations and other benefits have also contributed to the "work or no work" calculus.

These policies may be well intended, but they are not helping alleviate the labor shortage that is hobbling our recovery and complicating supply issues. Biden needs to fix this.

Cawthorn, Lee introduce bills banning interstate travel vaccine...

NYC extends vaccine mandate to expand to all public workers, ends...

Biden recently tweeted: "We need to reward work in this country—not just wealth."

We applaud that notion, and would celebrate a White House that is indeed rewarding, and even encouraging, work. The Biden White House is doing anything but, and it is hurting our recovery.

Liz Peek is a former partner of major bracket Wall Street firm Wertheim & Company. Follow her on Twitter @lizpeek.

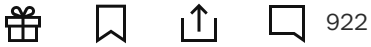
Exhibit S

The Washington Post Democracy Dies in Darkness

Border arrests have soared to all-time high, new CBP data shows

By Nick Miroff

Today at 9:28 a.m. EDT



CORRECTION

A previous version of this story incorrectly stated that Border Patrol arrests along the Mexico border reached their highest levels since 1986. Historic data shows fiscal year 2021's figure was the highest total ever recorded. The article has been corrected.

U.S. authorities detained more than 1.7 million migrants along the Mexico border during the 2021 fiscal year that ended in September, and arrests by the Border Patrol soared to the highest levels ever recorded, according to unpublished U.S. Customs and Border Protection data obtained by The Washington Post.

Illegal crossings began rising last year but skyrocketed in the months after President Biden took office. As CBP arrests increased this past spring, Biden described the rise as consistent with historic seasonal norms. But the busiest months came during the sweltering heat of July and August, when more than 200,000 migrants were taken into custody.

During a confirmation hearing Tuesday for Chris Magnus, the Tucson police chief Biden has nominated to lead CBP, Republican senators pressed him to characterize the surge as a "crisis."

Magnus called it a "significant challenge," echoing the Biden administration's preferred term, adding that "the numbers are very high." CBP is expected to release the 2021 fiscal year data later this week.

Border enforcement has become a major political liability for Biden, and the president's handling of immigration remains his worst-polling issue. He promised on the campaign trail to make the United States more welcoming to immigrants, in contrast to former president Donald Trump, whose zero-tolerance family separations generated widespread outrage in 2018.

During the transition, Biden said he wanted to move cautiously on immigration policy and avoid ending up "with 2 million people on our border."

Once in office, Biden quickly halted construction on the border wall, ended the "Remain in Mexico" policy, reversed key asylum restrictions and announced a 100-day pause on most deportations and enforcement by U.S. Immigration and Customs Enforcement.

Discover more of the stories that matter to you. Select your interests

them to stay. A tight U.S. labor market became another pull.

Earlier this year, Biden directed Vice President Harris to address the "root causes" of migration from Central America's Northern Triangle nations — Guatemala, Honduras and El Salvador. But the strategy has had little to no measurable effect, and Harris has distanced herself from the border and immigration issues generally.

The latest CBP data indicates that the administration's challenges extend far beyond Central America. Mexico was the single largest source of illegal migration during the 2021 fiscal year, as the Border Patrol arrested more than 608,000 Mexican nationals. That leaves the Biden administration in an awkward place, as it increasingly relies on Mexico to tighten enforcement and block caravan groups heading north.

Biden officials are in negotiations with Mexico to comply with federal court orders to restart the "Remain in Mexico" policy requiring asylum seekers to wait outside U.S. territory while their cases are processed.

The second-largest grouping was composed of migrants from outside Mexico and Central America whom CBP categorized as "other," including Haitians, Venezuelans, Ecuadorans, Cubans, Brazilians and migrants from dozens of other nations. They accounted for 367,000 arrests.

They were followed by migrants from Honduras (309,000), Guatemala (279,000) and El Salvador (96,000).

More than 1.3 million migrants have been taken into custody along the southern border in the nine months since Biden took office, including 192,000 last month, the latest CBP figures show.

In the fiscal years between 2012 and 2020, border arrests averaged about 540,000. The 2021 figure was more than three times that amount and the second-highest annual total ever recorded.

The extraordinary influx has produced a series of crises for the administration, starting this spring with record numbers of unaccompanied minors crossing without parents who were crowded shoulder to shoulder into Border Patrol tents.

Crossings by Central American family groups overwhelmed U.S. agents this summer, and in September, the sudden arrival of 15,000 mostly Haitian migrants to a crude camp in Del Rio, Tex., produced politically damaging scenes of chaos and harsh enforcement tactics by Border Patrol agents on horseback.

Immigrant advocates who backed Biden's candidacy have soured on his presidency lately, with several staging a virtual walkout last weekend during a meeting with White House policy advisers. Biden's proposals for a major immigration overhaul are stalled in Congress, and Republicans are planning to use his border record as a cudgel in next year's midterm elections.

The Biden administration has responded to criticism of the arrest numbers by noting that it continues to use the Title 42 public health policy to rapidly "expel" most adult border crossers to Mexico or their home countries.

Of the 1.7 million detained during the 2021 fiscal year, 61 percent were expelled under Title 42, the CBP data shows.

The expulsions have led to a significant increase in repeat crossing attempts by migrants who are turned back, so the number of distinct individuals taken into custody is lower than the number of arrests recorded. Recidivism rates have exceeded 25 percent in recent months, twice as high as in previous years, according to CBP figures.

The 1.7 million figure includes migrants arrested between ports of entry by the Border Patrol as well as those who

Discover more of the stories that matter to you. Select your interests

That exceeds the 1.64 million taken into custody in 2000 along the Mexico border, according to historic data.

CBP's Rio Grande Valley sector was the busiest during the 2021 fiscal year, with 549,000 Border Patrol apprehensions, followed by the Del Rio sector, with 259,000, which eclipsed historically busier sectors such as El Paso and Tucson.

The CBP figures show declines in seizures of cocaine, heroin and methamphetamine. Analysts attribute the decrease to diminished vehicle traffic through ports of entry as a result of pandemic-related travel restrictions, as well as fewer interdictions by overstretched border agents.

By Nick Miroff

Nick Miroff covers immigration enforcement and the Department of Homeland Security for The Washington Post. He was a Post foreign correspondent in Latin America from 2010 to 2017, and has been a staff writer since 2006. Twitter

Discover more of the stories that matter to you. Select your interests

Exhibit T

What is Smallpox?

Before smallpox was eradicated, it was a serious infectious disease caused by the **variola virus**. It was contagious—meaning, it spread from one person to another. People who had smallpox had a fever and a distinctive, progressive skin rash.

Most people with smallpox recovered, but about 3 out of every 10 people with the disease died. Many smallpox survivors have permanent scars over large areas of their body, especially their faces. Some are left blind.

Thanks to the success of vaccination, smallpox was eradicated, and no cases of naturally occurring smallpox have happened since 1977. The last natural outbreak of smallpox in the United States occurred in 1949.

Page last reviewed: June 7, 2016

Content source: Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of High-Consequence Pathogens and Pathology (DHCPP)

Exhibit U

Received: 19 January 2021 | Revised: 21 February 2021 | Accepted: 14 March 2021

DOI: 10.1111/eci.13554

REVIEW ARTICLE

WILEY

Reconciling estimates of global spread and infection fatality rates of COVID-19: An overview of systematic evaluations

John P. A. Ioannidis

Departments of Medicine, of Epidemiology and Population Health, of Biomedical Data Science, and of Statistics, and Meta-Research Innovation Center at Stanford (METRICS), Stanford University, Stanford, CA, USA

Correspondence
John P. A. Ioannidis, SPRC, 1265 Welch Road, Medical School Office Building Room X306, Stanford, CA 94305, USA.
Email: jioannid@stanford.edu

Funding information
None; the Meta-Research Innovation Center at Stanford (METRICS) has been funded with grants from the Laura and John Arnold Foundation.

Abstract

Background: Estimates of community spread and infection fatality rate (IFR) of COVID-19 have varied across studies. Efforts to synthesize the evidence reach seemingly discrepant conclusions.

Methods: Systematic evaluations of seroprevalence studies that had no restrictions based on country and which estimated either total number of people infected and/or aggregate IFRs were identified. Information was extracted and compared on eligibility criteria, searches, amount of evidence included, corrections/adjustments of seroprevalence and death counts, quantitative syntheses and handling of heterogeneity, main estimates and global representativeness.

Results: Six systematic evaluations were eligible. Each combined data from 10 to 338 studies (9-50 countries), because of different eligibility criteria. Two evaluations had some overt flaws in data, violations of stated eligibility criteria and biased eligibility criteria (eg excluding studies with few deaths) that consistently inflated IFR estimates. Perusal of quantitative synthesis methods also exhibited several challenges and biases. Global representativeness was low with 78%-100% of the evidence coming from Europe or the Americas; the two most problematic evaluations considered only one study from other continents. Allowing for these caveats, four evaluations largely agreed in their main final estimates for global spread of the pandemic and the other two evaluations would also agree after correcting overt flaws and biases.

Conclusions: All systematic evaluations of seroprevalence data converge that SARS-CoV-2 infection is widely spread globally. Acknowledging residual uncertainties, the available evidence suggests average global IFR of ~0.15% and ~1.5-2.0 billion infections by February 2021 with substantial differences in IFR and in infection spread across continents, countries and locations.

KEYWORDS

bias, COVID-19, global health, infection fatality rate, meta-analysis, seroprevalence

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2021 The Authors. *European Journal of Clinical Investigation* published by John Wiley & Sons Ltd on behalf of Stichting European Society for Clinical Investigation Journal Foundation

Highlights

- Six systematic evaluations have evaluated seroprevalence studies without restrictions based on country and have estimated either total number of people infected or aggregate infection fatality rates for SARS-CoV-2.
- These systematic evaluations have combined data from 10 to 338 studies (9-50 countries) each with partly overlapping evidence synthesis approaches.
- Some eligibility, design and data synthesis choices are biased, while other differing choices are defendable.
- Most of the evidence (78%-100%) comes from Europe or the Americas.
- All systematic evaluations of seroprevalence data converge that SARS-CoV-2 infection has been very widely spread globally.
- Global infection fatality rate is approximately 0.15% with 1.5-2.0 billion infections as of February 2021.

1 | INTRODUCTION

The extent of community spread of SARS-CoV-2 infection and the infection fatality rate (IFR) of COVID-19 are hotly debated. Many seroprevalence studies have provided relevant estimates. These estimates feed into projections that influence decision-making. Single studies create confusion, since they leave large uncertainty and unclear generalizability across countries, locations, settings and time points. Some overarching evaluations have systematically integrated data from multiple studies and countries.[1-6] These synthetic efforts probe what are typical estimates of spread and IFR, how heterogeneous they are, and what factors explain heterogeneity. An overview of these systematic evaluations comparing their methods, biases and inferences may help reconcile their findings on these important parameters of the COVID-19 pandemic.

2 | METHODS

2.1 | Eligible articles

Articles were eligible if they included a systematic review of studies aiming to assess SARS-CoV-2 seroprevalence; there were no restrictions based on country; and an effort was made to estimate either a total number of people infected or aggregate IFRs. Articles were excluded if they considered exclusively studies of particular populations at different risks of infection than the general population (eg only healthcare workers), if they focused on specific countries (by eligibility criteria, not by data availability), and if they made no effort to estimate total numbers of people infected and/or aggregate IFRs.

2.2 | Search strategy

Searches were updated until 14 January 2021 in PubMed, medRxiv and bioRxiv with 'seroprevalence [ti] OR fatality [ti] OR immunity [ti]' For feasibility, the search in PubMed was made more specific by adding '(systematic review OR meta-analysis OR analysis)'. Communication with experts sought potentially additional eligible analyses (eg unindexed influential reports).

2.3 | Extracted information

From each eligible evaluation, the following information was extracted:

1. Types of information included (seroprevalence, other)
2. Date of last search, search sources and types of publications included (peer-reviewed, preprints, reports/other)
3. Types of seroprevalence designs/studies included
4. Number of studies, countries, locations included
5. Seroprevalence calculations: adjustment/correction for test performance, covariates, type of antibodies measured, seroreversion (loss of antibodies over time)
6. Death count calculations: done or not; adjustments for over- or under-counting, time window for counting COVID-19 deaths in relationship to seroprevalence measurements
7. Quantitative synthesis: whether data were first synthesized from seroprevalence studies in the same location/country/other level; whether meta-analyses were performed across locations/countries and methods used; handling of heterogeneity, stratification and/or regression analyses, including subgroups

8. Reported estimates of infection spread, under-ascertainment ratios (total/documented infections) and/or IFR
9. Global representativeness of the evidence: proportion of the evidence (weight, countries, studies or locations, depending on how data synthesis had been done) from Europe and North America (sensitivity analysis: Europe and America)

2.4 | Comparative assessment

Based on the above, the eligible evaluations were compared against each other with focus on features that may lead to bias and trying to decipher the direction of each bias.

3 | RESULTS

3.1 | Eligible evaluations

Nine potentially eligible articles were retrieved[1-3,5-10] And four were rejected (Figure 1).[7-10] One more eligible report[4] was identified from communication with experts. The six eligible evaluations are named after their first authors or team throughout the manuscript.

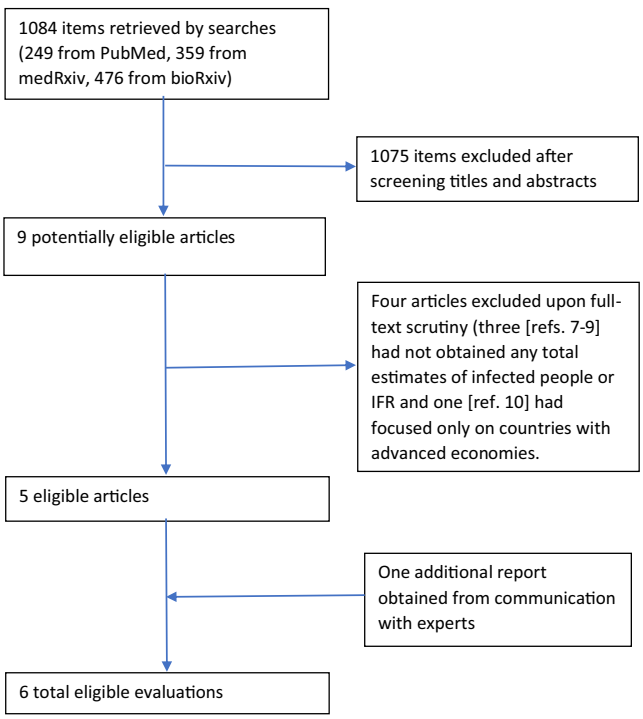


FIGURE 1 Flow diagram

3.2 | Information used

Five evaluations included only seroprevalence studies (Table 1). Meyerowitz-Katz also included non-serological and modelling papers; summary IFR was smaller in the seroprevalence studies (0.60% vs 0.84% in others). The six evaluations differed modestly in dates of last search (range, 6/16/2020-9/9/2020) and in sources searched. Given that few studies outside of Europe and Americas were released early, evaluations with earlier searches have a more prominent dearth of low-IFR studies from countries with younger populations and fewer nursing home residents.

Eligibility criteria varied and were sometimes unclear or left room for subjectivity. Consequently, eligible studies varied from 10 to 348 and countries covered with eligible data varied from 9 to 50. Two evaluations[1,4] excluded studies in overtly biased ways, leading to inflated IFR estimates.

Specifically, Meyerowitz-Katz excluded one study with low-IFR[5] alluding that the study itself 'explicitly warned against using its data to obtain an IFR'[1]; as co-investigator of the study, both myself and my colleagues are intrigued at this claim. They also excluded two more studies with low-IFR alluding that it 'was difficult to determine the numerator (ie number of deaths) associated with the seroprevalence estimate or the denominator (ie population) was not well defined',[1] while one even presented IFR estimates in its published paper. Another excluded paper[11] tabulated several seroprevalence studies with median IFR = 0.31%, half the Meyerowitz-Katz estimate.

The Imperial College COVID-19 Response Team (ICCRT) excluded studies with <100 deaths at the sero-survey mid-point.[4] This exclusion criterion introduces bias since number of deaths is the numerator in calculating IFR. Exclusion of studies with low numerator excludes studies likely to have low IFR. Indeed, five of six excluded studies with <100 deaths (Kenya, LA County, Rio Grande do Sul, Gangelt, Scotland)[12-16] have lower IFR than the 10 ICCRT-included studies; the sixth (Luxembourg)[17] is in the lower range of the 10 ICCRT-included studies.

The six evaluations varied on types of populations considered eligible. Table 2 summarizes biases involved in each study population type. General population studies are probably less biased, provided they recruit their intended sample. Conversely, studies of healthcare workers,[18] other high-risk exposure workers and closed/confined communities may overestimate seroprevalence; these studies were generally excluded, either upfront (5/6 evaluations) or when calculating key estimates (Bobrovitz). Other designs/populations may be biased in either direction, more frequently towards underestimating seroprevalence.[19-26] Three evaluations (Meyerowitz-Katz, ICCRT, O'Driscoll) were very aggressive with exclusions.

TABLE 1 Key features for eligible systematic data syntheses

Features	Meyerowitz-Katz	Rostami	Bobrovitz	Imperial college COVID-19 response team	Ioannidis	O'Driscoll
Types of information included	SP, non-serological and modelling studies	SP studies	SP studies	SP studies	SP studies	SP studies
Last search	16 June	14 August	28 August	Unclear	9 September	Unclear (1 September?)
Search sources	PubMed, preprints (medRxiv, SSRN), Google, Twitter searches, government agency reports eligible	PubMed, Scopus, EMBASE, medRxiv, bioRxiv, research reports eligible	MEDLINE, EMBASE, Web of Science, and Europe PMC, Google, communication with experts	SeroTracker searches (see Bobrovitz)	PubMed (LitCOVID), medRxiv, bioRxiv, Research Square, national reports, communication with experts for additional studies	Unclear
Types of SP studies included	Excluded targeted populations with selection bias, also four other studies[a]	Excluded at-risk populations (eg HCW), known diseases (eg dialysis, cancer)	All studies included if they reported on sample, date, region and SP estimate	Studies with defined sampling framework, defined geographic area, with availability of test performance, preferentially validation done as part of the study (not just by manufacturers), >100 deaths at SP study mid-point[b]; excluded healthcare workers, symptoms of COVID-19, self-referral or self-selection, narrow age range, confined settings, clinical samples	General population or approximations (including blood donors, excluding high risk, eg HCW, communities), sample size >500, area with population >5000	Unclear, but eventually it includes some general population studies, some blood donors and some hospital samples
Number of studies, countries, locations	24-27 studies[c], of which 16 serological from 14 countries	107 data sets from 47 studies from 23 countries	338 studies (184 from general population) from 50 countries (36 from general population)[d]	10 studies (six national, four subnational), nine countries[e]	82 estimates, 69 studies, 51 locations, 36 countries (main analysis at the location level)	25 studies from 20 countries (only 22 national representing 16 countries used in the ensemble model)
Studies published in peer-review journals at the time of the evaluation	1/16	61/107	4/40 included in final analysis of under-ascertainment ratio	5/10	35/82	6/20 countries

Abbreviations: HCW, healthcare workers; IFR, infection fatality rate; SP, seroprevalence.

[a]One study (LA County)[12] with very low IFR was excluded with the justification that it 'explicitly warned against using its data to obtain an IFR'; as a co-investigator of the study, both myself and my colleagues are intrigued at the rationale for exclusion; in the publication of the study in JAMA,[12] we did list limitations and caveats, as it is appropriate for any seroprevalence study to do; excluding studies that are honest to discuss limitations would keep only the worst studies that discuss no limitations. Two other studies with low IFR were excluded as well. One was done in Rio Grande do Sul[13] where its authors even report IFR estimates in their paper (0.29%, 0.23%, 0.38% in the three rounds of the serosurvey); the other was done in Boise,[85] where its authors properly discuss limitations but an approximation of IFR is possible; even if not perfectly accurate, it is certainly lower than the IFR estimates included in the Meyerowitz-Katz meta-analysis. For the fourth excluded study,[11] the justification offered for its exclusion is that it 'calculated an IFR, but did not allow for an estimate of confidence bounds'.[1] However, this study presents results of a New York study that Meyerowitz-Katz did include in their meta-analysis. Of note, that fourth study[11] also presents a cursory review of seroprevalence studies arriving at a median IFR = 0.31%, half of the summary estimate of Meyerowitz-Katz.; [b]Clear bias introduced since number of deaths is the numerator itself in the calculation of IFR, and exclusion of studies with low numerator is thus excluding studies likely to have low IFR; [c]Different numbers provided by the authors for total studies in abstract (n = 24), text of the paper (n = 25), tabulated studies (n = 27) and forest plot studies (n = 26); [d]39 estimates from 17 countries used in main calculation of median under-ascertainment ratio (N. Bobrovitz, personal communication); [e]One of the 10 included studies violates the eligibility criterion of the investigators having validated themselves the antibody test used; the ICCRT included this study invoking validation data for the same antibody kit done by a different team in a study in a completely different setting and continent (San Francisco); based on this rationale, perhaps many other studies could have been included, if the same violation of the eligibility criteria was tolerated. The included study was an Italian survey[30] which had only been released in the press with a preliminary report at the time of the ICCRT evaluation and which included crude results on only 64 660 of the intended 150 000 participants (missingness 57%). Its inferred IFR estimate (2.5%) is an extreme outlier, as it is 2- to 20-fold larger than other typical estimates reported from numerous European countries. Moreover, that IFR estimate even matches/exceeds case fatality rates, and thus, it is simply impossible. It is widely accepted that IFR must be several times smaller than case fatality rate, even in locations with substantial testing. Italy had very limited testing in the first wave and modest testing in the second wave. One estimate suggests that the number of infections in Italy at the peak of the first wave was 12 times more than the number of documented cases; that is, the IFR would be more than an order of magnitude lower than the case fatality rate.[31]

TABLE 2 Direction of potential bias in studies with different types of populations

Type of sampling	Direction of bias
General population (entire population or design for representative sample)	Depends on characteristics of individuals who cannot be reached and/or decline participation. If they are more likely to be more disadvantaged (eg have no address/phone/e-mail) and thus also at higher risk of infection, SP may be underestimated. Potential for bias is more prominent when non-response/non-participation is larger. Institutionalized populations and homeless people are typically not included, and these populations often have very high infection rates[19,20] ; thus, SP is underestimated
Convenience sample (including self-referral and response to adverts)	Bias could be in either direction. Volunteer bias is common and would tend to recruit more health-conscious, low-risk individuals,[21] leading to SP underestimation. Conversely, interest to get tested because of worrying in the presence of symptoms may lead to SP overestimation
Blood donors	Bias could be in either direction, but SP underestimation is more likely, since blood donors tend to be more health-conscious and thus more likely to avoid also risky exposures. An early classic assessment[22] described blood donors as 'low-risk takers, very concerned with health, better educated, religious, and quite conservative'—characteristics that would lead to lower infection risk. In countries with large shares of minorities (eg USA and UK), minorities are markedly under-represented among blood donors.[23,24] For example, in the USA, donation rates are 37%-40% lower in blacks and Hispanics versus whites[23] and in the UK, donation rates range from 1.59 per 1000 among Asian Bangladeshi origin, compared to 22.1 per 1000 among white British origin.[24] These minorities were hit the most by COVID-19. In European countries, donations are lower in low-income and low-education individuals[25,26] ; these are also risk factors for COVID-19 infection. Bobrovitz[3] found median seroprevalence of 3.2% in blood donor studies versus 4.1% in general community/household samples (risk ratio 0.80 in meta-regression). SP may be overestimated if blood donation is coupled to a free COVID-19 test in a poor population (as in the case of a study in Manaus, Brazil)
Clinical residual samples and patients (eg dialysis, cancer, other)	Bias could be in either direction, but SP underestimation is more likely since patients with known health problems may be more likely to protect themselves in a setting of a pandemic that poses them at high risk. Conversely, repeated exposure to medical facilities may increase risk. Demographic features and socio-economic status may also affect the size and direction of bias. Bobrovitz[3] found median seroprevalence of 2.9% in studies of residual samples versus 4.1% in general community/household samples (risk ratio 0.63 in meta-regression). Hospital visitors' studies had even lower seroprevalence (median 1.4%)
Healthcare workers, emergency response, other workers with obvious high risk of exposure	Bias very likely to lead to SP overestimation compared with the general population, because of work-related contagion hazard; however, this may not always be the case (eg most infections may not happen at work) and any increased risk due to work exposure sometimes may be counterbalanced by favourable socio-economic profile for some healthcare workers (eg wealthy physicians). Bias may have been more prominent in early days of the pandemic, especially in places lacking protective gear. Across eight studies with data on healthcare workers and other participants, seroprevalence was 1.74-fold in the former.[3]
Other workers	Bias could be in either direction and depends on work experience during the pandemic period and socio-economic background; for example, SP may be underestimated compared with the general population for workers who are wealthy and work from home during the pandemic and overestimated for essential workers
Communities (shelters, religious, other shared-living)	Likely very strong bias due to high exposure risk leading to SP overestimation compared with the general population. Some of these communities were saturated with very high levels of infection very early.[19,20]

Note: Abbreviations: SP, seroprevalence.

ICCRT had the most draconian exclusion criteria, excluding 165/175 identified seroprevalence studies. However, ICCRT actually dropped many general population studies (for various reasons), but included two blood donor studies[27,28] (out of many such) and one New York study[29] with convenience samples of volunteers recruited while entering grocery stores and through an in-store flyer. The latter inclusion goes against the stated ICCRT eligibility criteria where self-selection is reason for exclusion. The New York study[29] had high IFR (from the worst-hit state in the first wave). The preliminary press-released report from an Italian general population survey[30] was included in violation of ICCRT eligibility criteria[4] that a study should have performed its own antibody test validation; ICCRT 'salvaged' the Italian study by transporting validation data from another study in San Francisco. The Italian study report[30] showed data on only 64 660 of the intended 150 000 participants (missingness 57%). Its inferred IFR estimate (2.5%) is an extreme outlier (2- to 20-fold larger than other reported European estimates) and simply impossible: it matches/exceeds case fatality rates despite probably major under-ascertainment of infections in Italy.[31]

Finally, the six evaluations differed markedly on how many included seroprevalence estimates came from peer-reviewed publications (journal articles listed in the references) at the time of the evaluation: from only one peer-reviewed estimate in Meyerowitz-Katz to 61 in Rostami. Some included

TABLE 3 Adjustments and corrections for seroprevalence and death counts

Features	Meyerowitz-Katz	Rostami	Bobrovitz	Imperial College COVID-19 response team	Ioannidis	O'Driscoll
Adjustment of SP for test performance	Unclear selection rule	Unclear selection rule	Yes (Bayesian)	Yes	Yes, when done by authors of SP study	Yes (24/25 studies)
Adjustment of SP for confounders	Unclear selection rule	Unclear selection rule	Unclear selection rule	Unclear selection rule	Selecting most fully adjusted SP estimated	Unclear selection rule
Other SP correction	No	No	No	Seroreversion	Type of antibodies[a]	Seroreversion, in secondary analysis
Death count adjustments	No adjustments	Deaths not assessed	Deaths not assessed	No adjustments	No adjustments	No adjustments
Time window for death counts	10 d after completion of SP study	Deaths not assessed	Deaths not assessed	Distributional (truncated Gaussian and beta), mean 18.3 d from onset to seroconversion, 19.8 d from onset to death	7 d after mid-point of SP survey or as chosen by its authors	Distributional (gamma), mean 10 d from onset to seroconversion, 20 d from onset to death

Abbreviations: d, days; IFR, infection fatality rate; SP, seroprevalence.
[a]one-tenth adjustment per each not tested antibody (IgG, IgM, IgA).

seroprevalence estimates that came from preprints/reports published in peer-reviewed journals by 2/2021; final publications could have minor/modest differences versus preprints/reports. Even journal-published estimates may get revised; for example, a re-analysis increased Indiana seroprevalence estimates by a third.[32]

3.3 | Seroprevalence and death calculations

Three evaluations[3,4,6] routinely adjusted for test performance, one[5] adjusted for test performance when the authors of the studies had done so, and two were unclear (Table 3). Depending on test sensitivity/specificity, lack of adjustment may inflate or deflate seroprevalence. Ioannidis selected the most fully adjusted seroprevalence estimate, when both adjusted and unadjusted estimates existed; other evaluations were unclear on this issue. Ioannidis corrected the seroprevalence upward when not all three types of antibodies (IgG, IgM, and IgA) were assessed. ICCRT and O'Driscoll considered seroreversion adjustments.

Rostami and Bobrovitz did not collect death counts to estimate IFR. The other four evaluations did not systematically adjust death counts for under- or over-counting. Finally, ICCRT and O'Driscoll used distributional approaches on the time window for counting deaths (with means between seroconversion and death differing by 1.5 and 10 days, respectively), Ioannidis counted deaths until 7 days after the survey mid-point (or the date survey authors made a strong case for), and Meyerowitz-Katz counted deaths up until 10 days after survey end.

3.4 | Quantitative synthesis, heterogeneity and main estimates

The six evaluations differed in quantitative synthesis approaches with implications for the main results (Table 4).

Meyerowitz-Katz used random effects meta-analysis of 26 IFRs calculating a summary estimate despite extreme between-study heterogeneity (I^2 = 99.2%). Such extreme heterogeneity precludes obtaining meaningful summary estimates. Estimates from the same country/location were not combined first, and two multiply-counted countries (Italy and China) have high IFRs entered in calculations. Meta-analysis limited to seroprevalence studies yielded slightly lower summary IFR (0.60% vs 0.68%), but extreme between-study heterogeneity persisted (I^2 = 99.5%); thus, summary estimates remained meaningless. Extreme between-study heterogeneity persisted also within three risk-of-bias categories (I^2 = 99.6%, 98.8% and 94.8%, respectively), within Europe and within America. There was no between-study heterogeneity for four Asian estimates, but none came from

TABLE 4 Quantitative synthesis approaches, stratification and/or regression and main estimates

	Meyerowitz-Katz	Rostami	Bobrovitz	Imperial College COVID-19 response team	Ioannidis	O'Driscoll
Quantitative synthesis	26 IFR estimates combined at one step with D-L RE model, $I^2 = 99.4\%$	First step 107 SP estimates combined separately for each country with D-L RE model, then per region. Also D-L RE for all 107 estimates, $I^2 = 99.7\%$	Median SP calculated overall and per subgroup of interest.	Log-linear model for pooling age-stratified IFR, then age-stratified estimates extrapolated to the age structure of populations of typical countries	First step, sample size-weighted summary of SP per location; then median estimated across locations	The ensemble model eventually models age-stratified IFR in a total of 45 countries with available age-stratified death counts, but data are used as input from only 16 countries that have IFR data with some age stratification
Stratification and/or regression	Subgroup analyses per continent, month of publication, modelling versus serological and risk of bias	Subgroup analyses per age, gender, type of population, serological method, race/ethnicity, income, human development index, latitude/longitude, humidity, temperature, days from onset of pandemic; also RE meta-regressions	Subgroup analyses per GBD region, scope (national, regional, local, sublocal), risk of bias, days since 100th case (also explored in meta-regressions); RE inverse variance meta-analysis of prevalence ratios for demographics (age, sex, race, close contact, HCW status) with $I^2 = 85.1\%$-99.4% per grouping factor	Focus on age-strata, also IFR estimates with and without seroreversion, and (for some countries) excluding nursing home deaths	Separate analyses for age <70 years; also subgroup analyses according to level of overall mortality in the location	Focus on age-strata; also per sex/gender and per country
Main estimates	Summary IFR 0.68 (95% CI-0.53%-0.82%), 0.60 when limited to serological studies	263.5 million exposed/infected at the time of the study based on the pooled SP from all 107 data sets; when estimated per region the total is 641 million[a]	643 million infected as of 17 November, based on estimated median under-ascertainment factor of 11.9 (using 9 d before study end date for PCR counts)[b]	Overall IFR: LIC 0.22 (0.14, 0.39), LMIC) 0.37 (0.25, 0.61), UMIC 0.57 (0.38, 0.92), HIC 1.06 (0.73, 1.64)	Over 500 million infected as of September 12 (vs 29 million documented cases) globally; median IFR 0.23% in the available studies (0.09% in locations with <118 deaths/million), 0.20% in locations with 118-500 deaths/million, 0.57% in locations with >500 deaths/million	5.27% of the population of the 45 modelled countries had been infected by 1 September

Abbreviations: IFR, infection fatality rate; RE, random effects; SP, seroprevalence.

[a]In millions: Europe+North America 47, East+South-East Asia 47, Latin America 9, South America 6, Sub Saharan Africa 62, Central and South Asia 446, North Africa and West Asia 24; [b]Median under-ascertainment was 14.5 overall based on 125 study estimates and 11.9 in national estimates, 15.7 in regional estimates and 24.0 in local estimates.

seroprevalence data and their IFR estimate (0.46%) is far higher than many subsequent Asian studies (outside Wuhan) using seroprevalence data[5] instead of modelling.

Rostami also performed random effects meta-analyses but more appropriately combined at a first step seroprevalence data from studies in the same country, and in the same region, a summary estimate across all 107 estimates in all countries was also obtained. The step-wise approach avoids the Meyerowitz-Katz analysis flaw. However, seroprevalence estimates may still vary extremely even within the same location, for example if done at different times. Moreover, the main estimate of the evaluation ('263.5 million exposed/infected at the time of the study') extrapolated to the global population the pooled estimate from all 107 data sets. The more appropriate estimate is a sum of the infected per country, or at least per region. Actually, the authors did calculate numbers of people exposed/infected per world region. The sum was 641 million, 2.5-fold larger. Moreover, these numbers did not reflect 'the time of the study': the 107 seroprevalence studies were done 2-6 months before the Rostami evaluation was written.

Bobrovitz calculated medians (overall and across several subgroups of studies), and Ioannidis calculated sample size-weighted means per location and then medians across locations. Their approaches avoid multiple counting of locations with many estimates available. Bobrovitz also performed random effects inverse variance meta-analysis of prevalence ratios for diverse demographics (age, sex, race, close contact, healthcare workers). The approach is defendable, since prevalence ratios were calculated within each study, but still very large between-study heterogeneity existed ($I^2 = 85.1\%$-99.4% per grouping factor) making results tenuous. Bobrovitz and Ioannidis reach congruent estimates for total number infected globally (643 million by November 17 and at least 500 million by September 12, respectively) with under-ascertainment ratios of 11.9 in November and 17.2 in September. Only the latter evaluation calculated IFRs (0.23% overall; 0.05% for those <70 years old).

ICCRT and O'Driscoll focused on age-stratified estimates. ICCRT extrapolated age-stratified estimates to the age structure of populations of typical countries, obtaining separate overall IFR estimates for low-income countries (0.22%), lower-middle–income countries (0.37%), upper-middle–income countries (0.57%) and high-income countries (1.06%). O'Driscoll made extrapolations to 45 countries estimating 5.27% of their population infected by 1 September.

3.5 | Global representativeness

Seroprevalence data lacked global representativeness. 72%-91% of the seroprevalence evidence came from Europe and North America (78%-100% from Europe or Americas)

TABLE 5 Global representativeness

	Meyerowitz-Katz	Rostami	Bobrovitz	Imperial College COVID-19 response team	Ioannidis	O'Driscoll[b]
Estimates (countries)[a]						
Europe	11 (11)	52 (13)	33 (13)	8 (7)	22 (21)	13 (13)
North America	3 (1)	22 (1)	1 (1)	1 (1)	15 (2)	1 (1)
Latin America	1 (1)	17 (2)	3 (1)	1 (1)	3 (3)	1 (1)
Asia	1 (1)	14 (5)	2 (1)	0 (0)	10 (9)	0 (0)
Africa	0 (0)	2 (2)	1 (1)	0 (0)	1 (1)	1 (1)
Oceania	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Information from Europe and North America	91% of weight	72% of data sets	85% of data sets (82% of countries)	90% of data sets	73% of location estimates	87% of countries
Information from Europe and America	98% of weight	85% of data sets	93% of data sets (87% of countries)	100% of data sets	78% of location estimates	94% of countries

[a]Geographic location of estimates (countries) included in main calculations.; [b]The extrapolated 45 countries on which age-stratified IFR estimates are obtained also include countries outside the regions that have at least one country represented (Pakistan, Philippines, Bangladesh, Indonesia, China, Thailand, South Korea, Japan) even though not directly measured in any of them.

(Table 5). Lack of representativeness was most prominent in Meyerowitz-Katz (only one estimate from Asia, none from Africa), ICCRT (no estimates from Asia or Africa) and O'Driscoll (only one estimate from Africa, no estimate from Asia). However, ICCRT extrapolated to all countries globally and O'Driscoll extrapolated to 45 countries including eight in Asia.

4 | DISCUSSION

This overview of six systematic evaluations of global spread and/or IFR of SARS-CoV-2 utilizing seroprevalence data highlights differences in methods, calculations and inferences. Several choices made by some evaluations led to bias. Other choices are defendable and reveal some unavoidable variability on how evidence on these important questions should be handled.

Choices that led to biased inflated IFR estimates are the inclusion of modelling estimates, inappropriate exclusion of low-IFR studies despite fitting stated inclusion criteria of the evaluators, inappropriate inclusion of high-IFR studies despite not fitting stated inclusion criteria, and using low death counts as exclusion criterion. Two evaluations (Meyerowitz-Katz and ICCRT) suffered multiple such problems each. These biases contributed to generate inflated and, sometimes, overtly implausible results. These two evaluations also narrowly selected very scant evidence (16 and 10 studies, including only one and five peer-reviewed articles, respectively), while hundreds of seroprevalence estimates are available.

Differences in types of study designs and populations considered eligible may be defended with various arguments by each evaluator. Studies of healthcare workers were consistently excluded. No consensus existed on studies of blood donors, clinical samples, workers at no obvious high-risk occupations and various convenience samples; these designs have variable reliability. Reliability increases with careful adjustment for sampling, demographics and other key factors and when missing data are limited. General population sampling is theoretically best, but general population studies may still suffer large bias from selective missingness. Unreachable individuals, institutionalized people and non-participating invitees are typically at higher infection risk; if so, some general population studies may substantially underestimate seroprevalence (overestimate IFR). For example, Meyerowitz-Katz included a Danish government survey press release[33] where only 1071 of 2600 randomly selected invitees participated (missingness 59%); the estimated IFR (0.79%) is probably substantially inflated.[6,28]

Differences may also ensue from seroprevalence adjustments for test performance and other factors.[34,35] Sometimes the change in estimated seroprevalence is substantial.[36-38] Special caution is needed with low seroprevalence.[39] When not all types of antibodies are assessed, a correction may also be useful. Adjustment for test performance may seemingly suffice. However, control samples used to estimate test sensitivity come from PCR-tested diagnosed patients, while missed diagnoses typically reflect asymptomatic or less symptomatic patients not seeking testing. Sensitivity may be much lower in these people, as many develop no or low-titre antibodies.[40,41] Seroreversion has a similar impact. Preliminary evidence suggests substantial seroreversion.[29,42-45] For example, among healthcare personnel, 28.2% seroreverted in 2 months (64.9% in those with low titres originally).[45] Only ICCRT and O'Driscoll considered corrections for seroreversion, but still did not allow for high seroreversion. All these factors would result in underestimating seroprevalence (overestimating IFR).

Both over- and under-counting of COVID-19 deaths (the IFR numerator) may exist,[46,47] varying across countries with different testing and death coding. Correction of COVID-19 death counts through excess deaths is problematic. Excess reflects both COVID-19 deaths and deaths from measures taken.[46-49] Year-to-year variability is substantial, even more so within age-strata. Comparison against averages of multiple previous years is naïve, worse in countries with substantial demographic changes. For example, in the first wave, an excess of 8071 deaths (SMR 1.03, 95% CI 1.03-1.04) in Germany became a deficit of 4926 deaths (SMR 0.98, 95% CI 0.98-0.99) after accounting for demographic changes.[50] The exact timepoint when deaths are counted may affect IFR calculations when surveys happen while many deaths are still accruing. All evaluations that counted deaths allowed for greater time for death to occur than for seroconversion, but Meyerowitz-Katz used a most extreme delay, considering deaths until 10 days after survey end. Surveys take from one day to over a month; thus, inferred sampling-to-death delay may occasionally exceed 6 weeks. Meyerowitz-Katz defends this choice also in another paper[10] choosing 4 weeks after the serosurvey mid-point. However, the argument (accounting for death reporting delays) is weak. Several situational reports plot deaths according to date of occurrence rather than date of reporting anyhow.[51] Moreover, infection-to-death time varies substantially and may be shorter in developing countries where fewer people are long-sustained by medical support.

Some quantitative synthesis approaches were problematic, for example calculating summary estimates despite $I^2 > 99\%$ or no data combination within the same country/location before synthesis across countries/locations. Another generic problem with meta-analysis of such data is that it penalizes better studies that allow more appropriately for uncertainty in estimates (eg by accounting for test performance and adjusting for important covariates). Studies with less rigorous or no adjustments may have narrower CIs (smaller variance, thus larger weight).[5] Finally, for IFR meta-analysis, studies

with few deaths may have higher variance (lower weight) and these studies may have the lowest IFR.

Age stratification for IFR estimation and synthesis is a reasonable choice to reduce between-study heterogeneity driven by steep COVID-19 death risk age gradient.[52] However, both analyses[4,6] that capitalized on granular age stratification made tenuous extrapolations to additional countries from thin or no data. ICCRT lacked seroprevalence data on low-income and lower-middle–income countries (~half the global population); upper-middle–income countries (~35% of global population) were only represented by one estimate from Brazil assuming IFR = 1%, exceeding twofold to fivefold other peer-reviewed estimates from Brazil.[13,53] Estimates used from high-income countries included an impossible Italian estimate (IFR = 2.5%)[30] and mostly non–peer-reviewed data. O'Driscoll was more careful, but still some IFR extrapolations appear highly inflated versus data from subsequently accrued seroprevalence studies. Their ensemble model assumed highest IFR in Japan (1.09%) and lowest in Kenya (0.09%) and Pakistan (0.16%). Currently, available seroprevalence studies from these countries show markedly lower IFR estimates: =<0.03%,[54-56] =<0.01%[14] and 0.04%-0.07%,[57,58] respectively. In Japan, infections apparently spread widely without causing detectable excess mortality.[54] In Kenya, under-ascertainment compared with documented cases was ~1000-fold.[14] While some COVID-19 deaths are certainly missed in Africa, containment measures are more deadly.[59]

All six evaluations greatly over-represented Europe and America. Only two (Rostami and Ioannidis) included meaningful amounts of data from Asia and Africa (still less than their global population share) in main estimate calculations. Currently, extensive data suggest high under-ascertainment ratios in Africa and many Asian countries[5,14,54-61] and thus much lower IFR in Asia (outside Wuhan) and Africa than elsewhere.

Quality of seroprevalence studies varies. Risk-of-bias assessments in prevalence studies are difficult. There are multiple risk-of-bias scales/checklists,[62-65] but bias scores do not translate necessarily to higher or lower IFR estimates, while assessors often disagree in scoring (Appendix S1).

Acknowledging these caveats, four of the six evaluations largely reach congruent estimates of global pandemic spread. O'Driscoll estimated 5.27% of the population of 45 countries had been infected by 1 September 2020, that is 180 million infected among 3.4 billion. Excluding China, the proportion of population infected among the remaining 44 countries would be ~9%, likely >10% after accounting for seroreversion. Countries not included among the 45 include some of the most populous ones with high infection rates (India, Mexico, Brazil, most African countries). Therefore, arguably at least 10% of the non-China global population (ie at least 630 million) would be infected as of 1 September. This is very similar to the Ioannidis (at least 500 million infected as of 12 September) and Rostami (641 million infected by summer, when numbers are added per region) estimates. The Bobrovitz estimate (643 million infected as of 17 November) should be increased substantially given that only 2 of 17 countries informing the calculated under-ascertainment ratio were in Asia or Africa, continents with much larger under-ascertainment ratios. National surveys in India actually estimated 60% seroprevalence in November in urban areas.[66] Therefore, probably infected people globally were ~1 billion (if not more) by 17 November (compared with 54 million documented cases). By extrapolation, one may cautiously estimate ~1.5-2.0 billion infections as of 21 February 2021 (compared with 112 million documented cases). This corresponds to global IFR ~0.15%—a figure open to adjustment for any over- and under-counting of COVID-19 deaths (Appendix S2).

Meyerowitz-Katz and ICCRT reach higher estimates of IFR, but, as discussed above, these are largely due to endorsing selection criteria focusing on high-IFR countries, violations of chosen selection criteria and obvious flaws that consistently cause IFR overestimation. Similar concerns apply to another publication with implausibly high age-stratified IFRs by Meyerowitz-Katz limited to countries with advanced economies, again narrowly selected some of the highest IFR locations and estimates.[12]

Even correcting inappropriate exclusions/inclusion of studies, errors and seroreversion, IFR still varies substantially across continents and countries. Overall average IFR may be ~0.3%-0.4% in Europe and the Americas (~0.2% among community-dwelling non-institutionalized people) and ~0.05% in Africa[14] and Asia (excluding Wuhan). Within Europe, IFR estimates were probably substantially higher in the first wave in countries like Spain,[67] UK[68] and Belgium[69] and lower in countries such as Cyprus or Faroe Islands (~0.15%, even case fatality rate is very low),[70] Finland (~0.15%)[71] and Iceland (~0.3%).[72] One European country (Andorra) tested for antibodies 91% of its population.[73] Results[73] suggest an IFR less than half of what sampling surveys with greater missingness have inferred in neighbouring Spain. Moreover, high seroreversion was noted, even a few weeks apart[73]; thus, IFR may be even lower. Differences exist also within a country; for example within the USA, IFR differs markedly in disadvantaged New Orleans districts versus affluent Silicon Valley areas. Differences are driven by population age structure, nursing home populations, effective sheltering of vulnerable people,[74] medical care, use of effective (eg dexamethasone)[75] or detrimental (eg hydroxychloroquine)[76] treatments, host genetics,[77] viral genetics and other factors.

Infection fatality rate may change over time locally[78] and globally. If new vaccines and treatments pragmatically prevent deaths among the most vulnerable, theoretically global IFR may decrease even below 0.1%. However, there are still uncertainties

both about the real-world effectiveness of new options, as well as the pandemic course and post-pandemic SARS-CoV-2 outbreaks or seasonal re-occurrence. IFR will depend on settings and populations involved. For example, even 'common cold' coronaviruses have IFR~10% in nursing home outbreaks.[79]

Admittedly, primary studies, their overviews and the current overview of overviews have limitations. All estimates have uncertainty. Interpretation unavoidably has subjective elements. This challenge is well-known in the literature of discrepant systematic reviews.[80-84] Cross-linking diverse types of evidence generates even more diverse eligibility/design/analytical options. Nevertheless, one should separate clear errors and directional biases from defendable eligibility/design/analytical diversity.

Allowing for such residual uncertainties, reassuringly the picture from the six evaluations assessed here is relatively congruent: SARS-CoV-2 is widely spread and has lower average IFR than originally feared, and substantial global and local heterogeneity. Using more accurate estimates of IFR may yield more appropriate planning, predictions and evaluation of measures.

ACKNOWLEDGEMENTS

I am grateful to Niklas Bobrovitz and Rahul Arora for offering clarifications on their important study.

CONFLICTS OF INTEREST

None.

DISCLOSURES

I am the author of one of the six evaluations assessed in this article.

ORCID

John P. A. Ioannidis https://orcid.org/0000-0003-3118-6859

REFERENCES

1. Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection fatality rates. *Int J Infect Dis*. 2020;101:138-148.
2. Rostami A, Sepidarkish M, Leeflang MMG, et al. SARS-CoV-2 seroprevalence worldwide: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2021;27(3):331-340. https://doi.org/10.1016/j.cmi.2020.10.020
3. Bobrovitz N, Arora RK, Cao C, et al. *Global seroprevalence of SARS-CoV-2 antibodies: a systematic review and meta-analysis*. medRxiv. 2020. https://doi.org/10.1101/2020.11.17.20233460
4. Imperial College COVID-19 response team. *Report 34: COVID-19 Infection Fatality Ratio: Estimates from Seroprevalence*. October 29, 2020.
5. Ioannidis JPA. The infection fatality rate of COVID-19 inferred from seroprevalence data. *Bull World Health Organ*. 2021;99:19-33F.
6. O'Driscoll M, Ribeiro Dos Santos G, Wang L, et al. Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature*. 2021;590(7844):140-145. https://doi.org/10.1038/s41586-020-2918-0
7. Franceschi VB, Santos AS, Glaeser AB, et al. Population-based prevalence surveys during the Covid-19 pandemic: a systematic review. *Rev Med Virol*. 2020;e2200. https://doi.org/10.1002/rmv.2200
8. Chen X, Chen Z, Azman AS, et al. *Serological evidence of human infection with SARS-CoV-2: a systematic review and meta-analysis*. medRxiv. 2020:2020.09.11.20192773.
9. Arora RK, Joseph A, Van Wyk J, et al. SeroTracker: A global SARS-CoV-2 seroprevalence dashboard. *Lancet Infect Dis*. 2021;(21):e76-e77.
10. Levin AT, Hanage WP, Owusu-Boaitey N, Cochran KB, Walsh SP, Meyerowitz-Katz G. Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. *Eur J Epidemiol*. 2020;35(12):1123-1138.
11. Wilson L. *SARS-CoV2 COVID-19 infection fatality rate implied by the serology antibody testing in New York City*. SSRN 2020; http://refhub.elsevier.com/S1201-9712(20)32180-9/sbref0350
12. Sood N, Simon P, Ebner P, et al. Seroprevalence of SARS-CoV-2-specific antibodies among adults in Los Angeles County, California, on April 10–11, 2020. *JAMA*. 2020;323(23):2425-2427.
13. Silveira MF, Barros AJD, Horta BL, et al. Population-based surveys of antibodies against SARS-CoV-2 in Southern Brazil. *Nat Med*. 2020;26(8):1196-1199.
14. Uyoga S, Adetifa IMO, Karanja HK, et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Kenyan blood donors. *Science*. 2021;371(6524):79-82.
15. Streeck H, Schulte B, Kümmerer BM, et al. Infection fatality rate of SARS-CoV2 in a super-spreading event in Germany. *Nat Commun*. 2020;11(1):5829.
16. Thompson C, Grayson N, Paton RS, Lourenco J, Penman BS, Lee L. *Neutralising antibodies to SARS coronavirus 2 in Scottish blood donors – a pilot study of the value of serology to determine population exposure*. medRxiv. 2020. https://doi.org/10.1101/2020.04.13.20060467
17. Snoeck CJ, Vaillant M, Abdelrahman T, et al. *Prevalence of SARS-CoV-2 infection in the Luxembourgish population: the CON-VINCE study*. medRxiv. 2020. https://doi.org/10.1101/2020.05.11
18. Galanis P, Vraka I, Fragkou D, Bilali A, Katelidou D. Seroprevalence of *SARS-CoV-2 antibodies and associated factors in health care workers: a systematic review and meta-analysis*. medRxiv. 2020; https://doi.org/10.1101/2020.10.23.20218289
19. Imbert E, Kinley PM, Scarborough A, et al. Coronavirus disease 2019 (COVID-19) outbreak in a San Francisco homeless shelter. *Clin Infect Dis*. 2020;ciaa1071. https://doi.org/10.1093/cid/ciaa1071
20. https://covidtracking.com/data/long-term-care. Accessed January 18, 2021.
21. Burnett JJ. Psychographic and demographic characteristics of blood donors. *J Consumer Res*. 1981;8:62-66.
22. Ganguli M, Lytle ME, Reynolds MD, Dodge HH. Random versus volunteer selection for a community-based study. *J Gerontol A Biol Sci Med Sci*. 1998;53(1):M39-M46.
23. Patel EU, Bloch EM, Grabowski MK. Sociodemographic and behavioral characteristics associated with blood donation in the United States: a population-based study. *Transfusion*. 2019;59(9):2899-2907.

24. Lattimore S, Wickenden C, Brailsford SR. Blood donors in England and North Wales: demography and patterns of donation. *Transfusion*. 2015;55:91-99.
25. Burgdorf KS, Simonsen J, Sundby A, et al. Socio-demographic characteristics of Danish blood donors. *PLoS One*. 2017;12:e0169112.
26. Volken T, Weidmann C, Bart T, Fischer Y, Klüter H, Rüesch P. Individual characteristics associated with blood donation: a cross-national comparison of the German and Swiss population between 1994 and 2010. *Transfus Med Hemother*. 2013;40(2):133-138.
27. Erikstrup C, Hother CE, Pedersen OBV, et al. Estimation of SARS-CoV-2 infection fatality rate by real-time antibody screening of blood donors. *Clin Infect Dis*. 2021;72(2):249–253.
28. Emmenegger M, De Cecco E, Lamparter D, et al. *Early plateau of SARS-CoV-2 seroprevalence identified by tripartite immunoassay in a large population*. medRxiv. 2020. https://doi.org/10.1101/2020.05.31
29. Rosenberg ES, Tesoriero JM, Rosenthal EM, et al. Cumulative incidence and diagnosis of SARS-CoV-2 infection in New York. *Ann Epidemiol*. 2020;48:23-29.e4.
30. *Primi risultati dell' indagine di sieroprevalenza sul SARS-CoV2*. https://www.istat.it/it/archivio/246156. Accessed January 20, 2021.
31. Russell TW, Golding N, Hellewell J, et al. Reconstructing the early global dynamics of under-ascertained COVID-19 cases and infections. *BMC Med*. 2020;18:332.
32. Yiannoutsos CT, Halverson PK, Menachemi N. Bayesian estimation of SARS-CoV-2 prevalence in Indiana by random testing. *Proc Natl Acad Sci USA*. 2021;118:e2013906118.
33. Statens Serum Institut. *De første foreløbige resultater af undersøgelsen for COVID-19 i befolkningen er nu klar*. https://www.ssi.dk/aktuelt/nyheder/2020/de-forste-forelobige-resultater-af-undersogelsen-for-covid-19-i-befolkningen-er-nu-klar. Accessed January 18, 2021
34. Burgess S, Ponsford MJ, Gill D. Are we underestimating seroprevalence of SARS-CoV-2? *BMJ*. 2020;370:m3364.
35. Deeks JJ, Dinnes J, Takwoingi Y, et al. Cochrane COVID-19 diagnostic test accuracy group. Antibody tests for identification of current and past infection with SARS-CoV-2. *Cochrane Database Syst Rev*. 2020;6:CD013652.
36. Bendavid E, Mulaney B, Sood N, et al. COVID-19 antibody seroprevalence in Santa Clara County, California. *Int J Epidemiol*. 2021;dyab010. https://doi.org/10.1093/ije/dyab010
37. Shakiba M, Nazemipour M, Salari A, et al. Seroprevalence of SARS-CoV-2 in Guilan Province, Iran, April 2020. *Emerg Infect Dis*. 2021;27(2):636-638.
38. Nawa N, Kuramochi J, Sonoda S, et al. *Seroprevalence of SARS-CoV-2 IgG antibodies in Utsunomiya City, Greater Tokyo, after first pandemic in 2020 (U-CORONA): a household- and population-based study*. medRxiv. 2020. https://doi.org/10.1101/2020.07.20.20155945
39. Cai B, Ioannidis JP, Bendavid E, Tian L. *Exact inference for disease prevalence based on a test with unknown specificity and sensitivity*. arXiv. 2020; https://arxiv.org/abs/2011.14423
40. Long Q-X, Tang X-J, Shi Q-L, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med*. 2020;26:1200-1204.
41. Solbach W, Schiffner J, Backhaus I, et al. Antibody profiling of COVID-19 patients in an urban low-incidence region in Northern Germany. *Front Public Health*. 2020;8:570543.
42. Stringhini S, Wisniak A, Piumatti G, et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. *Lancet*. 2020;396(10247):313-319.
43. Ibarrondo FJ, Fulcher JA, Goodman-Meza D, et al. Rapid decay of anti–SARS-CoV-2 antibodies in persons with mild covid-19. *N Engl J Med*. 383(11):1085-1087. https://doi.org/10.1056/NEJMc2025179
44. Shioda K, Lau MS, Kraay AN, et al. *Estimating the cumulative incidence of SARS-CoV-2 infection and the infection fatality ratio in light of waning antibodies*. medRxiv. 2020; 2020.11.13.20231266.
45. Self WH, Tenforde MW, Stubblefield WB, et al. Decline in SARS-CoV-2 antibodies after mild infection among frontline health care personnel in a multistate hospital network — 12 States, April–August 2020. *MMWR*. 2020;69:1762-1766. https://doi.org/10.15585/mmwr.mm6947a2
46. Ioannidis JPA. Global perspective of COVID-19 epidemiology for a full-cycle pandemic. *Eur J Clin Invest*. 2020;7:e13423.
47. VanderWeele TJ. Challenges estimating total lives lost in COVID-19 decisions: consideration of mortality related to unemployment, social isolation, and depression. *JAMA*. 2020;324:445-446.
48. Bauchner H, Fontanarosa PB. Excess deaths and the Great Pandemic of 2020. *JAMA*. 2020;324:1504-1505.
49. Woolf SH, Chapman DA, Sabo RT, Weinberger DM, Hill L. Excess deaths from COVID-19 and other causes, March-April 2020. *JAMA*. 2020;324(5):510-513.
50. Stang A, Standl F, Kowall B, et al. Excess mortality due to COVID-19 in Germany. *J Infect*. 2020;81(5):797-801.
51. Ioannidis JPA, Axfors C, Contopoulos-Ioannidis DG. Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters. *Environ Res*. 2020;188:109890.
52. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020;584(7821):430-436.
53. Buss LF, Prete CA Jr, Abrahim CMM, et al. Three-quarters attack rate of SARS-CoV-2 in the Brazilian Amazon during a largely unmitigated epidemic. *Science*. 2021;371(6526):288-292.
54. Hibino S, Hayashida K, Ahn AC, Hayashida Y. Dynamic change of *COVID-19 seroprevalence among asymptomatic population in Tokyo during the second wave*. medRxiv. 2020. https://doi.org/10.1101/2020.09.21.20198796
55. Takita M, Matsumura T, Yamamoto K, et al. Geographical Profiles of COVID-19 Outbreak in Tokyo: An analysis of the primary care clinic-based point-of-care antibody testing. *J Prim Care Community Health*. 2020;11:2150132720942695.
56. Doi A, Iwata K, Kuroda H, et al. *Estimation of seroprevalence of novel coronavirus disease (COVID-19) using preserved serum at an outpatient setting in Kobe, Japan: a cross-sectional study*. medRxiv. 2020. https://doi.org/10.1101/2020.04.26.20079822
57. Nisar I, Ansari N, Amin M, et al. *Serial population based serosurvey of antibodies to SARS-CoV-2 in a low and high transmission area of Karachi, Pakistan*. medRxiv. 2020. https://doi.org/10.1101/2020.07.28.20163451
58. Javed W, Baqar J, Abidi SHB, Farooq W. *Sero-prevalence findings from metropoles in Pakistan: implications for assessing COVID-19 prevalence and case-fatality within a dense, urban working population*. medRxiv. 2020; 10.1101/2020.08.13.20173914
59. Roberton T, Carter ED, Chou VB, et al. Early estimates of the indirect effects of the COVID-19 pandemic on maternal and child mortality in low-income and middle-income countries: a modelling study. *Lancet Glob Health*. 2020;8(7):e901-e908.
60. Poustchi H, Darvishian M, Mohammadi Z, et al. SARS-CoV-2 antibody seroprevalence in the general population and high-risk occupational groups across 18 cities in Iran: a population-based

cross-sectional study. *Lancet Infect Dis*. 2021;21(4):473-481. https://doi.org/10.1016/S1473-3099(20)30858-6
61. Abu Raddad LJ, Chemaitelly H, Ayoub HH, et al. *Characterizing the Qatar advanced-phase SARS-CoV-2 epidemic*. medRxiv. 2020; https://doi.org/10.1101/2020.07.16.20155317
62. Shamliyan T, Kane RL, Dickinson S. A systematic review of tools used to assess the quality of observational studies that examine incidence or prevalence and risk factors for diseases. *J Clin Epidemiol*. 2010;63:1061-1070.
63. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and incidence data. *Int J Evid Based Health*. 2015;13:147-153.
64. Munn Z, Moola S, Riitano D, Lisy K. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. *Int J Health Policy Manag*. 2014;3:123-128.
65. Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol*. 2012;65:934-939.
66. Ghosh A. *India is missing about 90 infections for every COVID case, latest government analysis shows*. https://theprint.in/health/india-is-missing-about-90-infections-for-every-covid-case-latest-govt-analysis-shows/567898/. Accessed January 18, 2021
67. Pollán M, Pérez-Gómez B, Pastor-Barriuso R, et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. *Lancet*. 2020;396(10250):535-544.
68. Ward H, Atchinson C, Whitaker M, et al. *Antibody prevalence for SARS-CoV-2 following the peak of the pandemic in England: REACT2 study in 100,000 adults*. medRxiv. 2020; https://doi.org/10.1101/2020.08.12
69. Herzog S, De Bie J, Abrams S, et al. *Seroprevalence of IgG antibodies against SARS coronavirus 2 in Belgium – a prospective cross sectional study of residual samples*. medRxiv. 2020; https://doi.org/10.1101/2020.06.08.20125179
70. Worldometer. *Cyprus and Faroe Islands*, www.worldometer.com, Accessed February 21, 2021.
71. Finland Department of Health and Welfare. *Weekly report of the population serology survey of the corona epidemic*. Helsinki: Finland Department of Health and Welfare. 2020. [Finnish]. https://www.thl.fi/roko/cov-vaestoserologia/seroreport_weekly.html Accessed January 18, 2021
72. Gudbjartsson DF, Norddahl GL, Melsted P, et al. Humoral immune response to SARS-CoV-2 in Iceland. *N Engl J Med*. 2020. NEJMoa2026116 [online ahead of print]. https://doi.org/10.1056/NEJMoa2026116 PMID: 32871063
73. Royo-Cebrecos C, Vilanova D, Lopez J, et al. *Mass SARS-CoV-2 serological screening for the Principality of Andorra*. Research Square. 2020.
74. Ioannidis JPA. Precision shielding for COVID-19: Metrics of assessment and feasibility of deployment. *BMJ Glob Health*. 2021;6:e004614.
75. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. *New Engl J Med*. 2021; 384: 693-697.
76. Axfors C, Schmitt AM, Janiaud P, et al. Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19: an international collaborative meta-analysis of randomized trials. *Nat Commun*. 2021. (in press).
77. Chen HH, Shaw DM, Petty LE, et al. Host genetic effects in pneumonia. *Am J Hum Genet*. 2021;108(1):194-201.
78. Ioannidis JPA, Axfors CA, Contopoulos-Ioannidis DG. Second versus first wave of COVID-19 deaths: shifts in age distribution and in nursing home fatalities. *Environ Res*. 2021;195:110856.
79. Veiga ABGD, Martins LG, Riediger I, Mazetto A, Debur MDC, Gregianini TS. More than just a common cold: endemic coronaviruses OC43, HKU1, NL63, and 229E associated with severe acute respiratory infection and fatality cases among healthy adults. *J Med Virol*. 2021;93(2):1002-1007.
80. Ioannidis JPA. Meta-research: the art of getting it wrong. *Res Synth Methods*. 2010;1:169-184.
81. Campbell J, Bellamy N, Gee T. Differences between systematic reviews/meta-analyses of hyaluronic acid/hyaluronan/hylan in osteoarthritis of the knee. *Osteoarthritis Cartilage*. 2007;15:1424-1436.
82. Jadad AR, Cook DJ, Browman GP. A guide to interpreting discordant systematic reviews. *Can Med Assoc J*. 1997;156:1411-1416.
83. Moayyedi P, Deeks J, Talley NJ, Delaney B, Forman D. An update of the Cochrane systematic review of *Helicobacter pylori* eradication therapy in nonulcer dyspepsia: resolving the discrepancy between systematic reviews. *Am J Gastroenterol*. 2003;98:2621-2626.
84. Linde K, Willich SN. How objective are systematic reviews? Differences between reviews on complementary medicine. *J Royal Soc Med*. 2003;96:17-22.
85. Bryan A, Pepper G, Wener MH, et al. Performance characteristics of the Abbott Architect SARS-CoV-2 IgG assay and seroprevalence in Boise. *Idaho. J Clin Microbiol*. 2020;58(8):e00941–20.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Ioannidis JPA. Reconciling estimates of global spread and infection fatality rates of COVID-19: An overview of systematic evaluations. *Eur J Clin Invest*. 2021;51:e13554. https://doi.org/10.1111/eci.13554

Exhibit V

combat COVID. hhs.gov

COVID-19 Information

x

Get the latest public health information from CDC
Get the latest research information from NIH | Español
Learn more about COVID-19 and you from HHS

NEWS: DailyMed Announcements

SEPTEMBER 13, 2021

Pfizer received FDA BLA license for its COVID-19 vaccine

Pfizer received FDA BLA license on 8/23/2021 for its COVID-19 vaccine for use in individuals 16 and older (COMIRNATY). At that time, the FDA published a BLA package insert that included the approved new COVID-19 vaccine tradename COMIRNATY and listed 2 new NDCs (0069-1000-03, 0069-1000-02) and images of labels with the new tradename.

At present, Pfizer does not plan to produce any product with these new NDCs and labels over the next few months while EUA authorized product is still available and being made available for U.S. distribution. As such, the CDC, AMA, and drug compendia may not publish these new codes until Pfizer has determined when the product will be produced with the BLA labels.

Return to News Index

NIH NLM

Exhibit W

Jun 30, 2021, 11:31pm EDT | 23,319 views

Why The Big Quit Is Happening And Why Every Boss Should Embrace It

Lisa Curtis Former Contributor
Small Business Strategy
Founder of Kuli Kuli, a mission-driven moringa food startup

Follow

Listen to article 5 minutes

GETTY

The tables have turned and the CEOs are the ones cowering in fear.

Just a few months ago most employees were clinging desperately to their jobs, scared that their company would be the next one to initiate a round of Covid layoffs or furloughs. No longer.

Now we've entered into the Hot Vax Summer era of hookups, quitting jobs and jumping into pools. Or in the case of one now famous Taco Bell employee, a large workplace sink.

Clearly, employers no longer hold the power. Instead of shying away from this new dynamic, I believe that bosses should embrace this change and meet their employees where they are.

First, a little background.

The Big Quit

The American "Big Quit," or "Great Resignation" is a post-widespread-vaccination phenomenon that is touching everyone from McDonalds workers to software engineers. A record 4 million people quit their jobs in April, many of them in low-paid, inflexible industries like retail.

The same thing is starting to happen in higher paid jobs. Polls show that nearly 40% of white-collar employees would rather leave their jobs than give up remote work, and even highly sought after companies like Apple are scrambling to avoid mass resignations from return-to-office policies.

MORE FOR YOU

How To Increase Client Success As A Small Creative Agency

8 Steps To Making A Consistent $10K A Month In Your 1-Person Creative Agency

AMC And GameStop: Will Meme Stocks Pop Again In June?

For many CEOs who've spent the past 16 months focused on how to prevent layoffs, this rise in resignations may feel like a slap in the face. Instead, it

should feel like a wake-up call to embrace the new humanization of work.

Forbes | Careers

Climb the Career Ladder with Forbes

Land the job, get a raise and learn to lead with our weekly newsletter.

Email address

Sign Up

You may opt out any time. By signing up for this newsletter, you agree to the Terms and Conditions and Privacy Policy

The Humanization of Work

Perhaps my favorite part of working remotely during Covid-19 has been the constant video parade of pets, partners and kids.

AD

Recently I took a Friday afternoon video call while sitting on the ground with my 9 month-old daughter as she happily played with her toys. About ten minutes into the call, she decided that my computer was the best toy,

began climbing on top of me, and with one spectacular dive into the keyboard, managed to hang up the call.

When I got back onto the call, the entire group was laughing. One of the fellow CEOs told me afterward that my video fiasco brought an immeasurable amount of much-needed joy to his week.

With so many white-collar workers working from home, there is no longer a separation between life and work. While this comes with its own set of challenges (read: baby hanging up your Zoom calls), it has also made many workers reconsider the type of work that works for them.

Workplace flexibility is the new money in today's post vaccine economy. It's the ability to walk your dog at 2 p.m., or drop off kids at 10 a.m. It's in folding laundry while on a conference call, or going on a run in between meetings. Working remotely has enabled many white-collar workers to feel like they no longer had to choose between their work, family and well-being.

Three Questions Bosses Should Be Asking Themselves

This new dynamic can be a challenge for bosses who are used to measuring productivity by seeing who's left in the office after 7 p.m. For those leaders and managers, I recommend asking three simple questions:

1) Did productivity of this person/team fall during quarantine? *Research shows that focus and productivity improved*

2) Do I need employees in the office full-time to reap the benefits of the office? *Many companies are embracing the 3-2 model of three days in the office, 2 days remote*

3) Am I willing to lose employees due to my remote work policies? *As discussed above, employees are serious about quitting in search of more workplace flexibility*

This is a moment for leaders to step up and reimagine how their workplace can be a flexible space. It's time to create a workplace that encourages both productivity and quality of life. It is my hope that more bosses will embrace the humanization of work before the big quit hits their office.

Follow me on Twitter or LinkedIn. Check out my website.

Lisa Curtis

Follow

I'm the Founder & CEO of Kuli Kuli, the leading brand pioneering a green superfood called moringa. I've taken the company from an idea I dreamed up in Peace Corps and...

Read More

Reprints & Permissions

ADVERTISEMENT

Exhibit X

May 10, 2021, 3:00 AM MST

How to Quit Your Job in the Great Post-Pandemic Resignation Boom

If you're ready to leave, here are some tips on engineering a smooth exit.

By Arianne Cohen

Your monthly limit of free content is about to expire. **Stay on top of historic market volatility. Try 3 months for ~~$105~~ $6. Cancel anytime.**

ILLUSTRATION: DEREK ABELLA FOR BLOOMBERG BUSINESSWEEK

LISTEN TO ARTICLE

Ready to say adios to your job? You're not alone

LISTEN TO ARTICLE

▶ 3:22

SHARE THIS ARTICLE

Share

Tweet

Post

Email

Ready to say adios to your job? You're not alone. "The great resignation is coming," says Anthony Klotz, an associate professor of management at Texas A&M University who's studied the exits of hundreds of workers. "When there's uncertainty, people tend to stay put, so there are pent-up resignations that didn't happen over the past year." The numbers are multiplied, he says, by the many pandemic-related epiphanies–about family time, remote work, commuting, passion projects, life and death, and what it all means–that can make people turn their back on the 9-to-5 office grind. We asked Klotz what to expect as the great resignation picks up speed.

• What are we going to see this summer with employees and organizations?

A lot of uncertainty, for both sides. Companies are figuring out how to maintain their cultures and employees, so many are offering multiple options: Do you want to come back full time? Work remotely? In-office three days a week? Four days? One day? It will be unclear whether these options will be permanent, making it difficult for employees to decide whether to stay or go.

• So will everyone just quit?

No. Plenty of employees don't really want to resign. If their company would let them keep working from home or do fewer hours, they would.

• Say I want to quit, like, right now. What should I do?

Give a lot of thought to the reasons. Are you just assuming your company won't work with you and let you work part time or remotely or take a sabbatical?

you work part time or remotely or take a sabbatical.

Make sure you fully understand your company's plans. For example, if everyone is ordered back to the office, and the top three performers say they're quitting, the organization may rethink.

• Should I quit before or after returning to the office?

Consider going back for at least a week or two. Think of it as a test of your hypothesis. Humans tend to be really bad at predicting how they'll actually feel.

• What should I say to co-workers?

Co-workers may be having the same thoughts. You can imagine one thinking, I don't really want to go back to the office, but at least Anthony will be there. And then I call to say I'm not coming back. Give her time for that difficult conversation.

• How does one do a pandemic resignation?

It's going to be particularly tempting to use electronic mediums, but our research has found that organizations and managers respond poorly to emailing a boss or leaving a note on her desk.

• So when I talk to my boss in person or on Zoom, what should I say?

That you tried it, and it isn't working for you. Your boss will view that in a more favorable light than simply not trying at all. Your reasons should be honest, but not all the reasons. For example, if the job doesn't provide meaning, that doesn't need to be said. Give specific reasons, like graduate school or the commute.

• Is texting or emailing about it risky because of forwards?

Try to control the communication that you give to your organization, your co-workers, and your leader. In email you can't control the tone, and it often comes off wrong. You want to resign in as positive a way as possible.

• Why bother to be so careful?

We're going to see lots of "boomerang" employees, who a year from now miss their jobs and decide their novel isn't going as well as expected. Being a boomerang employee works only if you leave on a very, very positive note.

Exhibit Y

Survey: Vaccine-or-Testing Mandate Will Be Difficult to Implement

By Allen Smith, J.D.
October 15, 2021

Nine out of 10 recently surveyed organizations said it will be somewhat or very challenging to implement the Biden administration's expected vaccine-or-testing requirements. These respondents so far have not mandated that their employees get the COVID-19 vaccine, but they do meet the criteria for needing to institute the requirements.

Feedback

President Joe Biden announced plans on Sept. 9 (www.shrm.org/resourcesandtools/hr-topics/talent-acquisition/pages/federal-vaccine-mandate.aspx) for a new rule requiring employers with at least 100 employees to mandate that their workers be vaccinated against COVID-19 or undergo weekly testing. The president also signed orders stipulating that most federal employees and federal contractors, as well as most health care workers across the country, be vaccinated.

The Society for Human Resource Management (SHRM) conducted the survey electronically to a random sample of active SHRM members from Sept. 27 through Sept. 30. The 1,289 respondents represented organizations of all sizes—from two to more than 25,000 employees—in a wide variety of industries across the U.S. SHRM also conducted a separate survey of 1,500 U.S. workers.

"Organizations are concerned about the challenges to implementing the new vaccine mandate during a time when there is a talent shortage in many industries," said Trent Burner, SHRM's vice president of research. "The majority of organizations say mandating the vaccine will impact their organization's recruitment, retention, morale and engagement, and business operations."

FEATURED RESOURCE CENTER

COVID-19 Vaccination Resources (www.shrm.org/hr-today/news/hr-news/Pages/COVID-19-Vaccination-Resources.aspx)

Organizations' Concerns

Of organizations that meet the criteria for the Biden administration's vaccine-or-testing requirement, 85 percent said the anticipated requirement will make retaining employees more difficult. Eighty-nine percent said some of their employees will quit due to the new mandate.

Seventy-eight percent of HR respondents said the vaccine-or-testing requirements will make attracting and hiring new employees more difficult, while 82 percent said the requirements will make maintaining morale and engagement more difficult.

Seventy-two percent said the vaccine-or-testing requirements will make maintaining regular business operations more difficult.

"The mere possibility of federal vaccine mandates has raised alarm among HR professionals about the possibility of employee turnover," said Mark Codd, SHRM-SCP, labor relations group director for Publix Super Markets Inc., headquartered in Lakeland, Fla.

"Many organizations have undertaken extensive and creative campaigns to increase the voluntary vaccination rate before any federal mandate is issued," he said. "Now is the time for HR professionals to leverage their knowledge of the workforce and creatively develop a persuasive campaign to increase vaccination—both for compliance as well as the health of their workforce."

The federal government's expected vaccine-or-testing mandate for medium and large employers should prompt an internal assessment of the workforce, Codd added. "It's important to know the percent currently vaccinated, as well as understanding the numerous reasons for vaccine hesitation. That information forms the basis for the company's likely numerous campaigns to address and eliminate each vaccine hesitancy."

There are many reasons why workers are hesitant to get vaccinated. "Whether it's cultural, gender reasons, compromised health, distrust, fear or any one or more of other reasons, HR professionals must be capable of addressing each," he said.

Employee Pushback

Feedback

Many employers gearing up for the vaccine-or-testing mandate are experiencing employee pushback.

While there has been some acquiescence among unvaccinated staff to get vaccinated, many of the employees who wanted the vaccine have had it for months, said Joyce Chastain, SHRM-SCP, a regulatory compliance consultant with The Krizner Group in Tallahassee, Fla. Many of "the ones who don't have it made a conscious decision to not get the vaccination," she said. "It wasn't about apathy. It was a choice."

Chastain said those same employees now have to decide among:

- Keeping their job.
- Lying about a sincerely held religious belief.
- Getting an inoculation that they think is suspect.

"Some of these unvaccinated employees are key to the organization's mission or success," she said. "That puts the organization in the position of losing critical staff."

If an employee is refusing a vaccination and not seeking an accommodation, federal contractors are creating a transition plan now rather than waiting until Dec. 8 (www.shrm.org/resourcesandtools/legal-and-compliance/employment-law/pages/coronavirus-federal-contractors-vaccination-due-date.aspx), the deadline for federal contractors to be vaccinated against COVID-19, Chastain added.

"They are hoping to mitigate against having so many exits on the same day," she said. "They are also hoping that by implementing the transition plan now, employees [will] take them seriously."

Workers' Thoughts on the Biden Announcement

In a separate SHRM survey of 1,500 U.S. workers conducted from Sept. 28 to Sept. 29, over half of respondents who are not fully vaccinated (52 percent) said they will likely quit their jobs if their employer requires them to get the vaccine as a condition of employment.

While 60 percent of surveyed employees supported the vaccine-or-testing announcement, 40 percent did not.

Workers in manufacturing (49 percent) and in wholesale trade, retail trade or transportation, and warehousing (48 percent) were the most likely to not support the Biden announcement, followed by workers in administrative and support services (44 percent) and in construction, utilities, agriculture and mining (43 percent).

Workers in the professional, scientific and technical services (75 percent) were the most likely to support the Biden announcement, followed by workers in information, finance and insurance, and real estate (67 percent) and in health care and social assistance (64 percent).

Marie LaMarche, SHRM-SCP, division director of labor relations for Virginia Mason Franciscan Health in Tacoma, Wash., said employers can address the challenges they face in implementing the vaccine-or-testing requirement by "truly preparing for how employees will disclose their vaccination status. Even that can be difficult to administer and track, particularly since many people have waited and may have gotten their first dose and not their second."

She added, "Although I am a proponent of vaccination, the heartfelt concern I have heard from some employees makes me understand that it can be a scary proposition to some. A lot of employees are worried or scared about losing their jobs along with being concerned about the effects of the vaccination."

Feedback

HR DAILY NEWSLETTER

News, trends and analysis, as well as breaking news alerts, to help HR professionals do their jobs better each business day.

CONTACT US (WWW.SHRM.ORG/ABOUT-SHRM/PAGES/CONTACT-US.ASPX) | 800.283.SHRM (7476)

© 2021 SHRM. All Rights Reserved

SHRM provides content as a service to its readers and members. It does not offer legal advice, and cannot guarantee the accuracy or suitability of its content for a particular purpose.

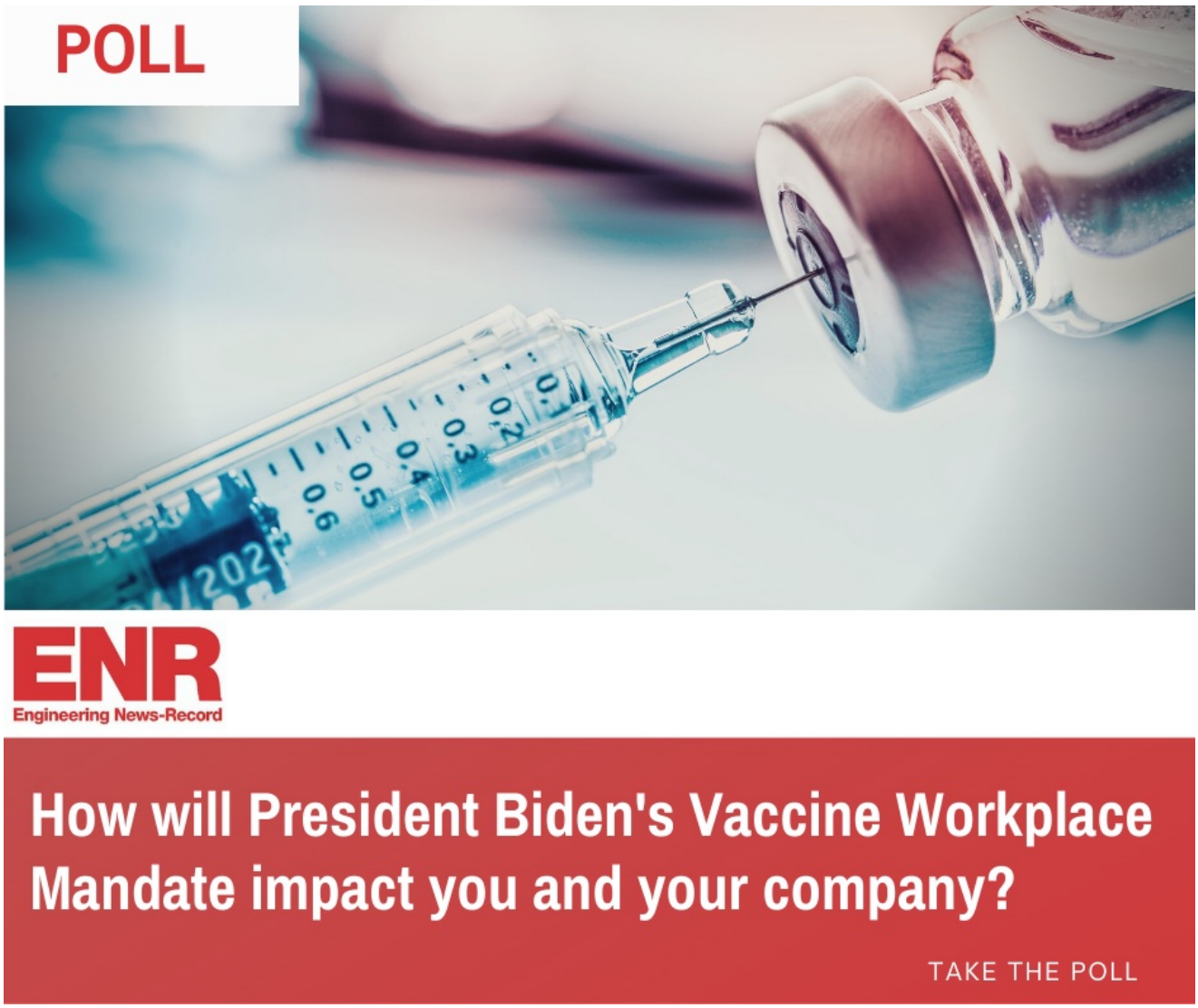
Disclaimer (www.shrm.org/about-shrm/Pages/Terms-of-Use.aspx#Disclaimer)

Exhibit Z

ENR
Engineering News-Record

Poll: President Biden's Vaccine Workplace Mandate

How will immunization requirements impact your workplace?



September 23, 2021

ENR Staff

Take the poll now.

With 46% of construction workers claiming they will not get vaccinated for Covid-19, President Joe Biden's Sept. 9 executive order requiring vaccines for all federal contractors and for companies wi more than 100 employees has become a concern for the Associated General Contractors and otl industry groups.

Privacy - Terms

"We expect to lose 40% of our workforce that will just quit in lieu of a vaccine mandate," says Ken Naquin, CEO of the Louisiana Associated General Contractors.

AGC has written letters to the administration expressing their concerns and local contractors fear they will lose more than 40% of their workforce to companies with fewer than 100 employees.

"AGC members justifiably fear that many of those workers, when faced with the choice between the vaccine and their job with a federal contractor, will quit and go to work for another contractor that does not have such a mandate," says a letter from AGC to the White House Safer Federal Workforce Task Force that will draft guidance.

"Because the vast majority of the construction industry is comprised of small businesses of fewer than 100 employees, and so many firms are looking for workers, those workers could very well go elsewhere and avoid both this federal contractor mandate and the testing mandate being put into effect for large employers by the U.S. Occupational Safety and Health Administration," AGC's letter continued.

Engineering News-Record would like to hear straight from the contractors and employees about how they plan to handle such a mandate, and what they, personally, will do if required to get a vaccine.

ENR wants to know whether and how a requirement for federal contractors and companies with more than 100 employees will impact you and your company. Please take our poll now!

Take our poll here.

The latest news and information

#1 Source for Construction News, Data, Rankings, Analysis, and Commentary

JOIN ENR UNLIMITED

Copyright ©2021. All Rights Reserved BNP Media.

Design, CMS, Hosting & Web Development :: ePublishing

Privacy - Terms