

Real-world study of effectiveness of Moderna COVID-19 vaccine under Emergency Use Authorization (EUA) and subsequent licensure - Draft

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a1. Background

Moderna plans to conduct a real-world observational study to evaluate the effectiveness of Moderna COVID-19 vaccine after an Emergency Use Authorization (EUA) is granted and subsequently licensed by the Food and Drug Administration (FDA) and after the Advisory Committee on Immunization Practice (ACIP) issues recommendations for COVID-19 vaccine prioritization and allocation. The study will be implemented in phases in accordance with ACIP recommendations and vaccine uptake.

We propose to conduct the study at Kaiser Permanente Southern California (KPSC). As one of the nation's largest not-for-profit integrated health care systems, KPSC provides an ideal environment for population-based vaccine research. The health plan's population includes more than 4.5 million Southern California residents ([Table 1](#)) who represent 260 different ethnicities and speak about 118 different languages. The large, diverse, and stable population facilitates the rapid accrual of a representative sample size and offers the ability to longitudinally evaluate long-term implications of immunization. Facilities include 15 hospitals and associated medical offices, all linked by an information infrastructure that supports both clinical practice and business needs.

Kaiser Permanente HealthConnect® is the largest and most advanced civilian electronic health record system available in the United States. In addition to supporting patient care, this robust system facilitates research, providing access to electronic health records (EHR) for the research team. The medical record number serves as a unique identifier linking all medical encounters for each member. Care received in the outpatient, inpatient, and emergency settings is documented in the EHR and captured in research databases. Care received outside the KPSC system is captured through claims. Details of care are available at the fingertips of researchers in near real time.

Immunizations are an important part of KPSC's overall focus on preventive care. The organization is one of the top-rated health maintenance organizations for meeting national standards of care, which include measures of childhood and adult immunization. Recommended vaccines are provided at no cost to KPSC members. KPSC thus provides an excellent real-world setting in which to understand the effectiveness of vaccines.

Our clinical databases include a variety of files that can be used for research:

- **Membership:** Includes demographic information such as sex, date of birth, and race/ethnicity.
- **Diagnosis:** Includes International Classification of Diseases, 10th revision (ICD-10) codes.

- **Procedure:** Includes ICD-10, Current Procedural Terminology (CPT), and Systematized Nomenclature of Medicine (SNOMED) codes.
- **Immunization:** Includes vaccine name, date of vaccination, route of administration, facility where vaccine was administered, dose, manufacturer, and lot number.
- **Laboratory:** Includes laboratory orders and results.
- **Pharmacy:** Includes National Drug Codes (NDC) and Generic Product Identifier (GPI) codes. More than 95 percent of members have a drug benefit with minimal copayments.
- **Mortality:** Includes deaths from hospital and membership databases, as well as from state and national death files.
- **Birth:** Includes pregnancy related information such as gestational age, birth weight, and Apgar scores.

Table 1: Demographic characteristics of Kaiser Permanente Southern California members on January 1, 2020

	Number of members
Total population	4,536,414
Sex:	
Male	2,201,661
Female	2,334,753
Age:	
Under 5 years	233,093
5 to 19 years	815,973
20 to 64 years	2,806,664
65 years and above	680,684
Race:	
White	2,522,389
Black or African American	486,761
American Indian & Alaska Native	28,326
Asian	676,123
Native Hawaiian and Other Pacific Islander	31,278
Other race	608,496
Two or more races	183,043
Ethnicity:	
Hispanic or Latinx (of any race)	1,914,756

2. COVID-19 at KPSC

At KPSC, diagnostic testing for SARS-CoV-2 is offered free of charge with an order from a KPSC physician. Prioritization for testing has evolved during the pandemic, with an emphasis on individuals with symptoms (particularly high-risk groups) and prior to hospital admissions or certain outpatient procedures. Testing is primarily conducted by RT-PCR of nasopharyngeal/oropharyngeal swabs on the Roche cobas[®] 6800 and 8800 analyzers or nasal/oropharyngeal swabs on Hologic Panther[®] analyzers. A smaller number of Abbott IDNOW[®] point-of-care tests are conducted in limited settings (e.g., obstetrics, pulmonary medicine, and infectious disease departments). Testing of asymptomatic individuals is also available, leveraging e-visits to place tests orders. Implementation in November 2020 of saliva testing and a new COVID-19 laboratory with Thermo Fisher Scientific Amplitude Solution instruments has increased testing capacity to approximately 46,000 tests per day.

As of 10/31/2020, over 600,000 SARS-CoV-2 RT-PCR tests have been performed at KPSC, of which 19% were among individuals ages ≥ 65 years (Table 2). There were 81,986 members testing positive (7,624 members ages ≥ 65 years). Additional members were diagnosed with COVID-19 based on positive test results outside of KPSC or clinical presentation and contact history, for a total of 24,320 members with a COVID-19 clinical diagnosis only. Approximately 31% (3,409/11,015) of COVID-19 patients ages ≥ 65 years were hospitalized, compared to only 5.7% (5,464/95,291) who were hospitalized among patients ages < 65 years. The proportion of COVID-19 patients being admitted to the ICU was 2.0% in patients < 65 years versus 11.1% in patients ≥ 65 years. The proportion of COVID-19 patients who died within 31 days after a COVID-19 diagnosis or a positive test was 0.39% in patients < 65 years vs. 9.1% in patients ≥ 65 years.

Table 2: COVID-19 molecular tests and diagnoses among members of Kaiser Permanente Southern California during 01/01/2020-10/31/2020

	Age (years)		Total
	< 65	≥ 65	
Number of patients tested for SARS-CoV-2 with RT-PCR test	515,664	123,129	638,793
Number of patients with positive SARS-CoV-2 RT-PCR test	74,362	7,624	81,986
Number of patients with a COVID-19 diagnosis ^a	95,291	11,015	106,306
Number of patients admitted to hospital with a COVID-19 diagnosis ^a	5,464	3,409	8,873
Number of patients admitted to ICU with a COVID-19 diagnosis ^a	1,913	1,220	3,133
Number of deaths within 31 days after the first COVID-19 diagnosis ^a	375	1,001	1,376

a. A COVID-19 diagnosis includes those with a positive SARS-CoV-2 RT-PCR test result or a COVID-19 diagnosis code only.

3. Planned sample size

We expect health care workers (HCWs) and adults ages ≥ 65 years to be included among the initial populations recommended by ACIP for COVID-19 vaccination during Phase 1, when COVID-19 vaccine supply may be limited. Therefore, we anticipate studying these two populations during Phase 1 of the proposed study. KPSC will aim to administer **750,000 doses (approximately 325,000 patients, assuming two doses per patient) of Moderna COVID-19 vaccine over the first 6 months after an EUA** is granted, based on calculations below:

- Approximately 730,000 members (50K HCWs and 680K adults ages ≥ 65 years)
- Reaching 35% coverage within 6 months ($730,000 \times 35\% = 255,500$)
- Times 2 doses (approximately 511,000 doses; this is over-estimating the 2-dose completion rate)
- Plus 20% buffer = $511,000 + 102,200 = 613,200$
- An additional 136,800 doses in case of increasing demand
- $613,200 + 136,800 = 750,000$

As this is a real-world study, KPSC will use the best available authorized/licensed ACIP-recommended COVID-19 vaccine product for our members.. The above sample size is a target for the time period under EUA, , and uptake will be driven by a number of factors including availability of COVID-19 vaccine, other COVID-19 vaccine products, ACIP prioritization, vaccine hesitancy, etc.

4. Methods

a. Overview

We propose a prospective cohort study to evaluate the vaccine effectiveness (VE) of Moderna COVID-19 vaccine in preventing laboratory confirmed or clinically diagnosed COVID-19 (COVID-19 diagnosis, hereafter), hospitalization for COVID-19, and mortality (in hospital or within 30 days after discharge). Comparison groups may include KPSC members of the same age who are not vaccinated with Moderna COVID-19 vaccine. The vaccinated subjects included in the study will be those receiving Moderna COVID-19 vaccine between January 1, 2021 (or possibly as early as December 2020) and December 31, 2021. The Phase 1 populations proposed by the ACIP COVID-19 Vaccines Work Group to receive COVID-19 vaccine first include health care personnel, long-term care facility residents, essential workers, adults with high-risk medical conditions, and adults ages ≥ 65 years. Considering the feasibility of identifying appropriate subjects for the study during Phase 1, we will include KPSC HCWs and adults ages ≥ 65 years. Vaccination can be expanded to other populations when further ACIP recommendations are issued and supply becomes adequate, which is expected to occur by the

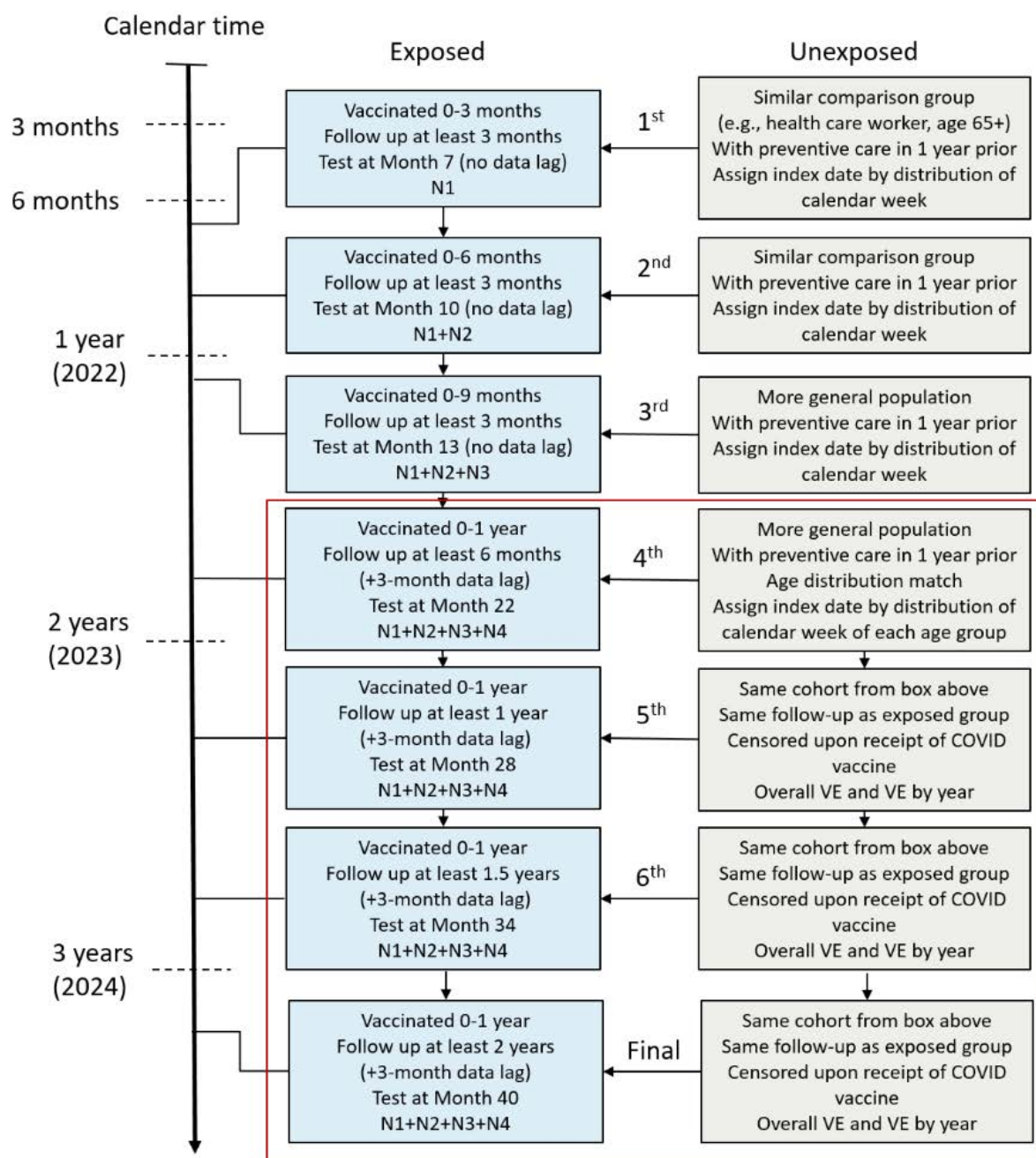
second half of 2021. The first vaccinated subject included in the study is expected to receive the first dose of Moderna COVID-19 vaccine in January 2021 (or possibly as early as December 2020) and the last subject will receive his/her 2nd dose of Moderna COVID-19 vaccine no later than December 31, 2021. The entire follow-up period will end on December 31, 2023. This would allow a maximum follow-up time of approximately almost 3 years.

In order to provide timely VE results during the accrual and follow-up period, we propose to perform interim analyses every 3 months in the first year starting from the 7th month of accrual (7/1/2021). In the first interim analysis, we will include vaccinated subjects that are accrued in the first ~3 months of the study (1/1/2021-3/31/2021) and followed for at least 3 months after completion of the 2nd dose. The second and third interim analyses will be performed in the 10th and 13th months with cumulative accrual from 1/1/2021-6/30/2021 and 1/1/2021-9/30/2021, respectively. Accrual will be finalized on December 31, 2021. The sequential interim analysis will be performed every 6 months in the second and the third year. The end-of-study analysis will be performed between April 1, 2024 and September 30, 2024. The final report will be submitted by the end of March 2025.

The comparison group will be a similar population (e.g. KPSC health care workers or adults 65 years and older) unvaccinated before the index date. An index date will be assigned to unvaccinated subjects based on the distribution of calendar time of vaccinated subjects on the vaccination (index) date. To be eligible for inclusion in the comparison group, subjects need to have received preventive care (e.g., influenza vaccine) within one year prior to the index date. For each interim analysis during the accrual period, the comparison group will be assessed and assigned with index dates independently based on all available data. Efforts will be devoted to control for potential confounders, risk for infection, and risk factors for severe outcomes. For example, the distribution matching on calendar time of index date will control for secular confounding of COVID-19 outcomes. Variables that will be considered as potential confounders for adjustment may include, age, sex, smoking history, functional status, race/ethnicity, body mass index, comorbidities, health care utilization (outpatient, Emergency Department, and inpatient visits), geographic area, influenza vaccination for the 2020-21 season, other vaccinations at baseline, and medical center.

The population of additional ages can be included in additional phases during the study period when new ACIP recommendations are issued. The overall study period can be extended to allow for additional follow-up time for populations that are included later.

Figure 1: Study design and analysis plan



b. Study Objectives

We propose to evaluate the vaccine effectiveness of Moderna COVID-19 vaccine at KPSC with the following objectives:

Primary Objective:

1. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis
2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease

Secondary Objectives:

1. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis by age and by sex
2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis by race/ethnicity groups
3. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in patients with chronic diseases (e.g. chronic kidney disease, chronic obstruction pulmonary disease (COPD), diabetes)
4. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis if given concomitantly with another vaccine
5. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis
6. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease
7. To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis
8. To evaluate the durability of 1 dose of Moderna COVID-19 vaccine in preventing severe COVID-19 disease

Primary Outcome

1. COVID-19 diagnosis will be defined as a COVID-19 positive molecular test or a diagnosis code
2. Severe COVID-19 disease includes hospitalization for COVID-19 (hospitalization within 7 days of a COVID-19 positive test/diagnosis or COVID-19 hospital discharge

diagnosis code) and COVID-19 mortality (in-hospital mortality and death within 30 days of hospital discharge)

Exposure

- CPT Vaccine code: 91301
- CVX code: 207
- Description: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5mL dosage, for intramuscular use
- Vaccine administration codes: 0011A (1st Dose), 0012A (2nd Dose)
- Manufacturer: Moderna, Inc
- Product name: Moderna COVID-19 Vaccine
- NDC 10/NDC 11 Labeler Product ID (vial): 80777-273-10 or 80777-0273-10
- Dosing interval: 28 Days

5. Timelines

Description	Estimated timeline
Final protocol submitted to CBER	March 1, 2021
Study completion date (End-of-study [final] analysis)	September 30, 2024
Final study report submission to CBER	June 30, 2025