NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	*Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California*
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Research question and objectives	The primary objective of this study is to estimate vaccine effectiveness (VE) of 2-doses of Pfizer's BNT162b2 (fully vaccinated) against acute respiratory illness requiring hospitalization due to SARS-CoV-2 infection among KPSC members ≥ 16 years of age. Secondary and exploratory objectives will examine VE for 1 dose vaccination, at least 1 dose, as well as against ED admission, specific variants and other populations of interest. To assess vaccine effectiveness (VE), we propose a large retrospective database study using two parallel study designs: a test-negative case-control design and a retrospective cohort design. We will conduct additional analyses of VE estimates by various patient characteristics and strain type.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ARI	Acute Respiratory Infection
BMI	body mass index
CAIR	California Immunization Registry
CHIP	Children's Health Insurance Program
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments of 1988
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	coronavirus Disease 2019
CSR	Clinical Study Report
ED	emergency department
EHR	electronic health record
EUA	Emergency Use Authorization
GEE	generalized estimating equations
HCW	health care worker
HR	hazard ratio
ICD	International Classification of Diseases
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KPSC	Kaiser Permanente Southern California
LOS	length of stay
LTCF	long term care facility
mRNA	modified ribonucleic acid
NIS	non-interventional study
NLP	Natural Language Processing
OR	odds ratio
PCR	polymerase chain reaction
PHI	protected health information
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis Software
SDIR	San Diego Immunization Registry
SOC	Standard of Care
TND	test-negative design

Abbreviation	Definition
US	United States
VE	vaccine effectiveness
WGS	whole genome sequencing

3. RESPONSIBLE PARTIES

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4. ABSTRACT

BNT162b2 is a modified RNA (mRNA) vaccine administered as 2 doses 21 days apart that encodes the full-length, membrane-anchored S glycoprotein of SARS-CoV-2 with two introduced proline mutations to lock it in the prefusion conformation. It was co-developed by BioNTech SE and Pfizer, Inc. The vaccine showed an acceptable safety profile in a Phase 1/2 study[1] and was tolerable and demonstrated a 95% clinical efficacy ≥7 days after the second dose against COVID-19 in persons without current or prior SARS-CoV-2 infection in a Phase 3 trial[2]. Pfizer-BioNTech 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 16 years of age and older. Data confirming the effectiveness of the vaccine outside of the clinical setting are needed.

The primary objective of this study is to estimate the vaccine effectiveness (VE) of 2-doses of Pfizer's BNT162b2 (fully vaccinated) vaccine against acute respiratory illness requiring hospitalization due to SARS-CoV-2 infection among KPSC members ≥ 16 years of age. Secondary and exploratory objectives will examine VE for 1 dose vaccination, at least 1 dose, as well as against emergency department (ED) admission, specific variants and other populations of interest.
To assess VE, we propose a large retrospective database study using two parallel study designs: a test-negative case-control design and a retrospective cohort design. The test-negative design (TND) will assess VE against COVID-19 hospitalization (primary endpoint) and

ED admission. The retrospective cohort analysis will assess VE against COVID-19 hospitalization (primary), ICU admission, death, ED admission, and outpatient disease (with no subsequent hospitalization within 14 days). We will further conduct additional analyses of VE estimates by various patient characteristics and strain type.

This study will be conducted at Kaiser Permanente Southern California (KPSC), an integrated health care organization comprising one of the largest health insurance plans in the US, a hospital system, and >7,600 physicians and 27,000 nurses located throughout 9 counties of Southern California. For the TND, the study population will include all KPSC patients 16 years or older who are admitted to the hospital or present to the ED with acute respiratory infection (ARI) after 14 December 2020 (date of first vaccinations at KPSC), and who receive a PCR test for SARS-CoV-2. For the Full Cohort Design, the study population will include all KPSC members as of 14 December 2020 (date of first Pfizer vaccination at KPSC) aged 16 and older.

Vaccine exposure for both study designs include fully vaccinated, defined as 2 doses of BNT162b2 received with ≥7 days between receipt of the 2nd dose and the event date (e.g., admission);partially vaccinated, defined as 1 dose (only) of BNT162b2 received with ≥14 days between the receipt of the 1st dose and the event date; and ever vaccinated, defined as ≥1 dose of BNT162b2 received with ≥14 days between the receipt of the 1st dose and the event date. The unexposed group will include individuals with no record of COVID-19 vaccination at the time of the event and will serve as the reference group in all VE analyses. All data will be collected from KPSC electronic health records (EHRs).

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned date
Start of data collection	01 April 2021
Final SAP	15 May 2021
Interim Data Analysis/Report 1	30 June 2021
Final Study Report on Primary Data Collection	30 July 2022
Secondary and exploratory data collection	30 July 2023
Final Clinical Study Report (CSR)	01 January 2024
Submit Manuscript for Publication	15 March 2024

7. RATIONALE AND BACKGROUND

The outbreak of the 2019 novel coronavirus disease (COVID-19), which is caused by severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), is still a pandemic threat to global public health. Although the epicenter of the COVID-19 outbreak in December of 2019 was in Wuhan, China, the disease has spread to more than 200 countries with more than 117 million confirmed cases and 2.6 million confirmed deaths worldwide as of 09 March 2019. In addition, essentially everyone's lives have been affected as a result of mandatory isolation and quarantine measures. The ripple effect of the COVID-19 outbreak has brought major challenges to health systems across the world and has had far-reaching impacts on the global economy. So far, public health experts have largely only been able to employ nonpharmaceutical intervention strategies to mitigate and control the spread of the virus. Now that safe and effective vaccines are available, further evaluation of their effectiveness outside of the clinical trial setting are needed following their introduction into the general population.

BNT162b2 is a modified RNA vaccine recommended as 2 doses 21 days apart that encodes the full-length, membrane-anchored S glycoprotein of SARS-CoV-2 with two introduced proline mutations to lock it in the prefusion conformation. It was co-developed by BioNTech SE and Pfizer, Inc. The vaccine showed an acceptable safety profile in a Phase 1/2 study[1]. In a Phase 3 trial, the vaccine was tolerable and demonstrated 95% efficacy $\geq$7 days after second dose against COVID-19 in persons without current or prior SARS-CoV-2 infection[2]. The vaccine is currently authorized for used 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 16 years of age and older and data confirming the effectiveness of the vaccine outside of the clinical setting are needed.

As such, this study will be conducted in Kaiser Permanente Southern California (KPSC), a large integrated healthcare organization with over 4.7 million members who comprise a socioeconomically diverse and broadly representative population that reflects of the racial/ethnic groups living in Southern California. As of 23 February 2021, KPSC has had over 441,000 COVID-19 cases and approximately 29,000 confirmed patients admitted to the hospital and has vaccinated more than 311,000 individuals. KPSC has 2 Regional Laboratories that process COVID-19 and other specimens. The central reference laboratories receive more than 50,000 specimens per day from the local laboratories and perform over 29 million tests annually. All laboratories undergo routine quality checks to meet or surpass accrediting body specifications.

8. RESEARCH QUESTION AND OBJECTIVES

The primary objective of the study is to estimate vaccine effectiveness (VE) of 2 doses of Pfizer's BNT162b2 vaccine (i.e., fully vaccinated) against acute respiratory illness (ARI) requiring hospitalization due to SARS-CoV-2 infection among KPSC members ≥16 years of age. VE will be evaluated using a test-negative design (TND), including all KPSC patients 16 years or older who are admitted to the hospital with acute respiratory infection (ARI) after 14 December 14 2020 (date of first vaccinations at KPSC), and who receive a PCR test for SARS-CoV-2. Secondary and exploratory objectives will examine VE for 1 dose vaccination, at least 1 dose, as well as against ED admission, specific variants and other populations of interest. Additionally, we will estimate VE using a full cohort design, including all KPSC members 16 years or older. Table 1 and Table 2 outline all primary, secondary and exploratory objectives for the current study for the TND and full cohort designs, respectively. Additional sensitivity analyses are not described below, but rather are outlined in the subsequent Analysis section. To assess VE, we propose a large retrospective database study using two parallel study designs: a test-negative case-control design and a retrospective cohort design. The test-negative design (TND) will assess VE against COVID-19 hospitalization (primary endpoint) and ED admission. The retrospective cohort analysis will assess VE against COVID-19 hospitalization (primary), ICU admission, death, ED admission, and outpatient disease (with no subsequent hospitalization within 14 days). We will further conduct additional analyses of VE estimates by various patient characteristics and strain type.

Table 1. TND Study Design Proposed Objectives

Test-Negative Design	
Objectives	Endpoints
Primary:	Primary:
1. To estimate the effectiveness of 2 doses of BNT162b2 (i.e., fully vaccinated) against hospitalization for ARI due to SARS-CoV-2 infection.	VE calculated as 1 minus the odds ratio (OR) comparing the odds of being fully vaccinated (2 doses) with BNT162b2 for hospitalized cases and controls, multiplied by 100%.
Secondary:	Secondary:
1. To estimate the effectiveness of 2 doses of BNT162b2 (i.e., fully vaccinated) against ED admission (without subsequent hospitalization) for ARI due to SARS-CoV-2 infection.	VE calculated as 1 minus the OR comparing the odds of being fully vaccinated (2 doses) with BNT162b2 for ED cases and controls, multiplied by 100%.
2. To describe the effectiveness of only 1 dose of BNT162b2 (i.e., partially vaccinated) against hospitalization for ARI due to SARS-CoV-2 infection.	VE calculated as 1 minus the OR comparing the odds of being partially vaccinated with BNT162b2 (only 1 dose) for hospitalized cases and controls, multiplied by 100%.
3. To describe the effectiveness of only 1 dose of BNT162b2 (i.e., partially vaccinated) against ED admission (without subsequent	VE calculated as 1 minus the OR comparing the odds of being partially vaccinated with BNT162b2 (only 1 dose) for ED cases and controls, multiplied by 100%.

Table 1. TND Study Design Proposed Objectives

Test-Negative Design	
hospitalization) for ARI due to SARS-CoV-2 infection.	
4. To describe the effectiveness of ≥1 dose of BNT162b2 (i.e., ever vaccinated) against hospitalization for ARI due to SARS-CoV-2 infection.	VE calculated as 1 minus the OR comparing the odds of ever being vaccinated (≥1 dose) with BNT162b2 for hospitalized cases and controls, multiplied by 100%.
5. To describe the effectiveness of ≥1 dose of BNT162b2 (i.e., ever vaccinated) against ED admission (without subsequent hospitalization) for ARI due to SARS-CoV-2 infection.	VE calculated as 1 minus the OR comparing the odds of ever being vaccinated (≥1 dose) with BNT162b2 for ED cases and controls, multiplied by 100%.
6. To further describe the effectiveness of BNT162b2 against hospitalization and ED admission stratified by prevalent or important viral strains	BNT162b2 VE estimates stratified by virus variant (as determined by genome sequencing) and select descriptive analyses described above
7. To evaluate the effectiveness of BNT162b2 against severe hospitalization-related outcomes (e.g., ICU admission, mechanical ventilation, and death)	BNT162b2 VE estimates against severe outcomes including ICU admission, mechanical ventilation, and death.
Tertiary/Exploratory:	Tertiary/Exploratory:
1. Compare VE of models stratified by relevant vaccination phase time periods to understand how VE may change as vaccinated patient risk profiles change over time.	BNT162b2 VE estimates by vaccination phase
2. To estimate the effectiveness of 1, ≥1, or 2 doses of BNT162b2 (i.e., fully vaccinated) against hospitalization or ED for ARI due to SARS-CoV-2 infection.	VE calculated as 1 minus the OR comparing the odds of have 2, 1, or ≥1 doses of BNT162b2 for hospitalized and ED cases and controls, multiplied by 100%.
3. To further describe the effectiveness of BNT162b2 against hospitalization and ED admission stratified by various patient characteristics (e.g., age, sex, race/ethnicity, chronic medical conditions, history of SARS-CoV-2 infection, long-term care facility residence, pregnancy status, and receipt of influenza vaccine).	BNT162b2 VE estimates by age group BNT162b2 VE estimates by sex BNT162b2 VE estimates by presence of chronic medical conditions, history of SARS-CoV-2 infection, pregnancy status BNT162b2 VE estimates by race/ethnicity BNT162b2 VE estimates by receipt of influenza vaccine in the last year BNT162b2 VE estimates among long-term care facility residents (hospital outcome only) BNT162b2 VE estimates by time since vaccination BNT162b2 VE estimates by time between first and second dose among those who received 2 doses
4. To describe the proportion of hospitalized and ED patients with ARI where SARS-CoV-2 was identified.	Proportion of ARI hospitalizations where SARS-CoV-2 is identified.

Table 1. TND Study Design Proposed Objectives

Test-Negative Design	
5. To summarize the proportion of patients who receive 0, 1, or 2 doses of BNT162b2 among hospitalized and ED patients. 6. To summarize the time between administration of the first and second dose of BNT162b2 among patients who received 2 doses 7. To summarize the time since vaccination with BNT162b2 (most-recent dose) since vaccinations at KPSC began	Proportion of patients who receive 0, 1, and 2 doses of BNT162b2 Average and median time between receipt of the first and second dose BNT162b2 among patients who received two doses Average and median time between 14 December 2020 and receipt of last dose among patients receiving BNT162b2
8. To describe demographic, clinical, and laboratory characteristics (i.e., viral strain) and disease severity of any BNT162b2 vaccine failures	Describe age, gender, race/ethnicity, clinical characteristics, and severity (ICU admission, ventilator, death) of any patients who received BNT162b2 and test positive for SARS-CoV-2
9. To describe COVID-19 disease severity for vaccinated and unvaccinated cases in the TND design	Describe disease severity for vaccinated and unvaccinated cases (e.g., average hospital length of stay (LOS), 30-day readmission, the proportion requiring ICU admission or mechanical ventilation, death)

Table 2. Full Cohort Study Design Proposed Objectives

Cohort Design	
Objectives	Endpoints
Primary:	Primary:
1. To estimate the effectiveness of 2 doses of BNT162b2 (i.e., fully vaccinated) against hospitalization due to SARS-CoV-2 infection.	VE calculated as 1 minus the hazard ratio (HR) comparing the incidence of being fully vaccinated (2 doses) with BNT162b2 for hospitalization due to SARS-CoV-2 infection and not, multiplied by 100%.
Secondary:	Secondary:
1. To estimate the effectiveness of 2 doses of BNT162b2 (i.e., fully vaccinated) against ED admission (without subsequent hospitalization) ED admission due to SARS-CoV-2 infection.	VE calculated as 1 minus the HR comparing the incidence of being fully vaccinated (2 doses) with BNT162b2 for ED admission due to SARS-CoV-2 infection and not, multiplied by 100%.
2. To estimate the effectiveness of 2 doses of BNT162b2 (i.e., fully vaccinated) against ICU admission due to SARS-CoV-2 infection	VE calculated as 1 minus the HR comparing the incidence of being fully vaccinated (2 doses) with BNT162b2 for ICU admission due to SARS-CoV-2 infection and not, multiplied by 100%.
3. To estimate the effectiveness of 2 doses of BNT162b2 (i.e., fully vaccinated) against death due to SARS-CoV-2 infection	VE calculated as 1 minus the HR comparing the incidence of being fully vaccinated (2 doses) with BNT162b2 for death due to SARS-CoV-2 infection and not, multiplied by 100%.

Table 2. Full Cohort Study Design Proposed Objectives

Cohort Design	
4. To estimate the effectiveness of 2 doses of BNT162b2 (i.e., fully vaccinated) against COVID-19 outpatient visits (without subsequent hospitalization within 14 days) due to SARS-CoV-2 infection	VE calculated as 1 minus the HR comparing the incidence of being fully vaccinated (2 doses) with BNT162b2 for COVID-19 outpatient visits (without subsequent hospitalization within 14 days) due to SARS-CoV-2 infection and not, multiplied by 100%.
5. To describe the effectiveness of only 1 dose of BNT162b2 (i.e., partially vaccinated) against hospitalization, ED admission, ICU admission, death, and outpatient visits (without subsequent hospitalization within 14 days) due to SARS-CoV-2 infection.	VE calculated as 1 minus the HR comparing the incidence of only 1 dose of BNT162b2 (i.e., partially vaccinated) for hospitalization, ED visit, death, and COVID-19 outpatient visits (without subsequent hospitalization within 14 days) due to SARS-CoV-2 infection and not, multiplied by 100%.
6. To describe the effectiveness of ≥1 dose of BNT162b2 (i.e., ever vaccinated) against hospitalization, ICU admission, ED admission, death, and outpatient visits (without subsequent hospitalization within 14 days) due to SARS-CoV-2 infection.	VE calculated as 1 minus the HR comparing the incidence ≥1 dose of BNT162b2 (i.e., ever vaccinated) for hospitalization, ED visit, death, and COVID-19 outpatient visits (without subsequent hospitalization within 14 days) due to SARS-CoV-2 infection and not, multiplied by 100%.
Tertiary/Exploratory:	Tertiary/Exploratory:
1. Compare VE of models stratified by relevant vaccination phase time periods to understand how VE may change as vaccinated patient risk profiles change over time.	BNT162b2 VE estimates by vaccination phase
2. To further describe the effectiveness of BNT162b2 by durability of vaccine effectiveness after receipt of 2 doses.	VE calculated as 1 minus the HR comparing the incidence of being fully vaccinated (2 doses) at various timepoints from vaccination for all outcomes, multiplied by 100%.
3. To further describe the effectiveness of BNT162b2 stratified by various patient characteristics (e.g., age, sex, race/ethnicity, chronic medical conditions, history of SARS-CoV-2 infection, long-term care facility residence, pregnancy status, and receipt of influenza vaccine).	BNT162b2 VE estimates by age group BNT162b2 VE estimates by sex BNT162b2 VE estimates by presence of chronic medical conditions, history of SARS-CoV-2 infection, pregnancy status BNT162b2 VE estimates by race/ethnicity BNT162b2 VE estimates by receipt of influenza vaccine in the last year BNT162b2 VE estimates among long-term care facility residents (hospital outcome only) BNT162b2 VE estimates by time since vaccination BNT162b2 VE estimates by time between first and second dose among those who received 2 doses
4. To summarize the proportion of patients who receive 0, 1, or 2 doses of BNT162b2 5. To summarize the time between administration of the first and second dose of BNT162b2 among patients who received 2 doses 6. To summarize the time since vaccination with BNT162b2 (most-recent dose) from study enrollment	Proportion of patients who receive 0, 1, and 2 doses of BNT162b2 Average and median time between receipt of the first and second dose BNT162b2 among patients who received two doses Average and median time between study enrollment and receipt of last dose among patients receiving BNT162b2

Table 2. Full Cohort Study Design Proposed Objectives

Cohort Design	
7. Estimate overall incidence rates by vaccination status and by important demographic and clinical characteristics	Incidence by vaccination status, age, gender, race/ethnicity, clinical characteristics outlined further below.
8. To further describe the effectiveness of BNT162b2 stratified by prevalent or important viral strains	BNT162b2 VE estimates stratified by virus variant (as determined by genome sequencing) and all descriptive analyses described above
9. To estimate the effectiveness of 2 doses of BNT162b2 (i.e., fully vaccinated) against death during hospitalization due to ARI due to SARS-CoV-2 infection	VE calculated as 1 minus the HR comparing the incidence of being fully vaccinated (2 doses) with BNT162b2 for death during hospitalization due to SARS-CoV-2 infection and not, multiplied by 100%.

9. RESEARCH METHODS

9.1. Research Setting

Kaiser Permanente Southern California (KPSC) is a large integrated healthcare delivery system that covers more than 4.7 million members. KPSC comprises one of the largest health insurance plans in the United States (US), a hospital system, and >7,600 physicians and 27,000 nurses located throughout 9 counties of Southern California. 15 medical centers and 234 medical offices comprise the KPSC clinical care setting. Kaiser Permanente Southern California's member population is socioeconomically diverse and broadly representative of the racial/ethnic groups living in Southern California**.** Our population represents > 260 ethnicities and > 150 languages spoken. As of December 2018, the majority of current members are Hispanic or Latino (43%), followed by White (35%), Asian/Pacific Islander (12%), Black or African American (9%), and Other (1%). Member retention is very high, with nearly 90% staying after 1 year, 78% remaining after 3 years, and 71% remaining after 5 years. Members enroll through the Kaiser Foundation Health Plan for prepaid health care insurance, including pharmaceutical benefits, through group plans, individual plans, Medicare, Medicaid, and other low-income programs. As of December 2018, 22% of patients were enrolled through Medicare or Medi-Cal and Children's Health Insurance Program (CHIP).

Our pre-paid system is a strong incentive to receive care within KPSC and members rarely seek outside care. KPSC provides care across the entire spectrum of healthcare needs, from outpatient, inpatient, ED, urgent care, specialty care, pharmacy, imaging, laboratory, virtual care, health education classes, and other services for our members. When clinical services sought outside of our system are captured through claims reimbursement requests.
Each Kaiser Permanente Southern California member is assigned a unique medical record number upon joining the health plan. This number is retained for life, irrespective of leaving and rejoining the health plan. This unique number allows for the linkage of different computer files containing clinical and administrative information. Kaiser Permanente HealthConnect®, our comprehensive electronic health record, is one of the largest private electronic health record systems in the world. Kaiser Permanente HealthConnect and our integrated model securely connect medical offices and hospitals across the region, providing members,

physicians, and other authorized health care providers with online access to clinical information. Kaiser Permanente HealthConnect is a customized version of the EPIC electronic health record.

The system integrates all aspects of care, including pharmacy and lab services, as well as appointments, registration, and billing. This information can be used for research purposes. Trained research staff have access to Kaiser Permanente HealthConnect through the Kaiser Permanente Regional Application Portal.

Regional Laboratories

The Sherman Way Regional Reference Laboratories is a clinical laboratory management system that interfaces with Kaiser Permanente's medical centers and medical office buildings. The central reference laboratory occupies more than 150,000 square feet of laboratory space and employs more than 600 employees. Services include comprehensive chemistry, microbiology, cellular pathology, cytogenetic testing, and anatomic pathology services based on state-of-the-art instrumentation and methodologies.

The Chino Hills reference laboratory occupies more than 120,000 square feet of laboratory space and employs approximately 230 employees. Services cover specimen processing, including send-outs, auto-chemistry, endocrinology, limited special chemistry, immunology, bacteriology, molecular microbiology, and histology.

The clinical laboratories located in the local medical centers and medical offices each routinely conduct 2,000 to 3,000 laboratory tests per day. The central reference laboratory receives more than 50,000 specimens per day from the local laboratories and performs over 29 million tests annually. All laboratories undergo routine quality checks to meet or surpass accrediting body specifications.

The Regional Reference Laboratories are fully accredited by the College of American Pathologists. They are licensed by the Department of Health and Human Services Centers for Medicare and Medicaid Services under the Clinical Laboratory Improvement Amendments (CLIA) of 1988, by the State of California Department of Public Health to perform clinical assays, and by the U.S. Food and Drug Administration Bureau of Biologics. They are inspected by the American Association of Blood Banks for handling of blood components.

There is a dedicated Regional Laboratory Operations team including management and Research Associates that supports research and serves as the liaison between Research & Evaluation and the Regional Laboratory.

COVID-19 at KPSC

As of 23February 2021 KPSC has had over 441,000 COVID-19 cases and approximately 29,000 confirmed patients admitted to the hospital. We have vaccinated more than 311,000 individuals as of 23 February 2021.

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 reverse transcriptase polymerase chain reaction (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.

9.2. Study design

This is a database only study of existing healthcare data, no patients will be actively enrolled.

Vaccine exposure for both study designs include fully vaccinated, defined as 2 doses of BNT162b2 received with ≥7 days between receipt of the 2nd dose and the event date (e.g., admission);partially vaccinated, defined as 1 dose (only) of BNT162b2 received with ≥14 days between the receipt of the 1st dose and the event date; and ever vaccinated, defined as ≥1 dose of BNT162b2 received with ≥14 days between the receipt of the 1st dose and the event date. The unexposed group will include individuals with no record of COVID-19 vaccination at the time of the event and will serve as the reference group in all VE analyses. All data will be collected from KPSC electronic health records (EHRs).

Study Design(s)

Test Negative Case-Control Design

A TND study design will be used to evaluate the primary objective of this study, to assess effectiveness of 2 doses of Pfizer COVID vaccine ≥7 days after second dose against hospitalization for ARI due to SARS-CoV-2 infection. It will include all KPSC patients 16 years or older who are admitted to the hospital with acute respiratory infection (ARI) after 14 December 2020 (date of first vaccinations at KPSC), and who receive a PCR test for SARS-CoV-2. For secondary objectives estimating VE against ED admission, the TND will include KPSC patients 16 years or older who present to the ED with acute respiratory infection (ARI) after 14 December 2020 and who receive a PCR test for SARS-CoV-2. These populations will be used to evaluate additional secondary and exploratory objectives outlined in Table 1 and Table 2 above, including VE of 1 dose or ≥1 dose and VE for important virus variants.

The index date will be defined as the date of hospitalization or ED admission. Patients can contribute more than one ARI event to the study if a subsequent ARI event for the same patient occurred >30 days after the previous event.

Per KPSC clinical protocol, we expect that ED patients with ARI will be tested for COVID-19, and in the inpatient setting, all patients with or without ARI will get tested for COVID-19 (to be confirmed with preliminary data). VE will be estimated separately for prevention of hospitalization (primary outcome) and for prevention of emergency department presentation without hospitalization (secondary outcome).

Full Cohort Design

A full cohort design will be used for secondary objectives to further explore BNT162b2 VE in the KPSC population. The cohort study will include all KPSC members as of 14 December 2020 (date of first Pfizer vaccination at KPSC) who are age 16 and older. The exposure will be receipt of Pfizer's COVID-19 vaccine, with separate relative VEs estimated for those with 2 doses, 1 dose, or ≥1 dose as in the TND design above. In this full cohort design, a patient's vaccination status, and thus exposure, will change over time, with all patients entering the cohort as unvaccinated. The outcomes of interest will be COVID-19 associated hospitalization, ED admission, ICU admission, death, and outpatient COVID-19 diagnoses (without subsequent hospitalization within 14 days). As with the TND, the main outcome of interest will be hospitalization, and the VE of focus will be 2 doses of BNT162b2. The full cohort analysis will serve as a secondary analysis and will allow for comparability with TND study methodology. Cohort members will be censored if they disenroll from KPSC, die for reasons not related to COVID-19 (death not within the 30 days following a positive COVID-19 laboratory test), receive any other newly licensed or investigational COVID-19 vaccine or prophylactic agent other than Pfizer's COVID-19 vaccine, receive >2 Pfizer COVID-19 vaccine doses, experience an outcome <14 days after receipt of the 1st Pfizer COVID-19 dose, or experience an outcome <7 days after receipt of the 2nd Pfizer COVID-19 dose.

9.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

Test Negative Design

1. KPSC patients 16 years or older who are admitted to the hospital (primary objective) with acute respiratory infection (ARI; ICD codes listed in Appendix Table 1) after 14 December 2020 (date of first vaccinations at KPSC), and who receive a PCR test for SARS-CoV-2.

2. For secondary objectives estimating VE against ED admission, the TND will include KPSC patients 16 years or older who present to the ED with ARI after 14 December 2020, and who receive a PCR test for SARS-CoV-2.

3. We will include membership requirement of 6 months prior to index date, which is defined as the date of hospitalization or ED admission (allowing 31-day administrative gap), to facilitate accurate capture of comorbid conditions.

Cohort Design

1. All KPSC members as of 14 December 2020 (date of first Pfizer vaccination at KPSC) who are age 16 and older.

2. For the cohort study, patients must have at least 6 months of membership (allowing 31-day administrative gap) prior to 14 December 2020 (index date, date vaccinations first began at KPSC) to facilitate accurate capture of comorbid conditions.

9.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

Test Negative Design

Patients who receive any other newly licensed or investigational SARS-CoV-2 vaccine or COVID-19 prophylactic agent other than Pfizer's COVID-19 vaccine prior to hospitalization (or ED, for secondary objective) will be excluded from the analysis. Patients will also be excluded if the index date is within certain time windows from vaccination date, outlined further in the exposure section below.

Cohort Design

There will be no exclusion criteria for the cohort design, however patients will be censored for receiving any other newly licensed or investigational SARS-CoV-2 vaccine or COVID-19 prophylactic agent other than Pfizer's COVID-19 vaccine. Patients will also be censored

if the event (hospitalization, ED encounter, etc.) occurs within certain time windows from vaccination date, outlined further in the exposure section below.

9.3. Variables

9.3.1. Test Negative Design Outcomes and Exposures

Cases: Cases will be defined as those with any positive KPSC laboratory-confirmed PCR test from a sample collected within 14 days prior to hospital admission through 3 days after a hospital admission (primary objective) or ED encounter (secondary objective) with an ARI code (Appendix Table 1).

Controls: Controls will be defined as those with laboratory confirmed negative COVID-19 (negative COVID-19 test during first 3 days of hospitalization for primary objective or ED admission for secondary objective and no positive COVID-19 tests within 30 days prior to encounter).

Exposure Definition: The exposure of interest is history of vaccination with BNT162b2. For the primary objective, patients will be considered vaccinated if they have documented evidence of receiving the second dose of BNT162b2 ≥7 days before index date (i.e., defined as the date of hospitalization or ED admission). When evaluating the effectiveness of 1 dose of BNT162b2, patients will be considered vaccinated if they have documented evidence of receiving the first dose of BNT162b2 ≥14 days before index date. Four levels of exposure variable will be assessed:

1. **Fully vaccinated** defined as 2 doses of BNT162b2 received with ≥7 days between receipt of the 2nd dose and the index date. This group will serve as the 'exposed' group evaluated in the primary objective. Patients who received only 1 dose or 2 doses of BNT162b2 with <7 days between receipt of the 2nd dose and the index date will be excluded from analysis. In sensitivity analyses, VE will also be calculated for 2 doses of BNT162b2 received with ≥14 days between receipt of the 2nd dose and the index date.

2. **Partially vaccinated** defined as 1 dose (only) of BNT162b2 received with ≥14 days between receipt of the 1st dose and the index date. This group will serve as the 'exposed' group as a secondary endpoint. Patients who received 2 doses or 1 dose of BNT162b2 with <14 days between receipt of the 1st dose and the index date will be excluded from analysis.

3. **Ever vaccinated** defined as ≥1 dose of BNT162b2 received with ≥14 days between index date and receipt of the 1st dose. Patients who received 1 dose of BNT162b2 received with <14 days between receipt of the 1st dose and the index date will be excluded from analysis

4. **Never vaccinated** defined as never received BNT162b2. This group will serve as the reference exposure group (i.e., 'unexposed' group) in all VE analyses.

The fully vaccinated (2 dose) exposure group will be considered for the primary objective, while the partially (1 dose) and ever vaccinated (≥1 dose) groups will be considered in secondary objectives.

9.3.2. Full Cohort Design Outcome and Exposures

Main outcome

The main outcome of interest will be COVID-19 hospitalization, which will be defined as a hospitalization with a positive PCR SARS-CoV-2 test within 14 days prior and 3 days after admission date.

Other outcomes of interest

COVID-19 ICU will be defined as time spent in an intensive care/critical care unit during a hospital stay with COVID-19 admit as defined above.

COVID-19 ED encounter, which will be defined as an ED encounter with a positive PCR SARS-CoV-2 test within 14 days prior and 3 days after encounter.

COVID-19 death will be defined as death within the 30 days following a positive COVID-19 laboratory test. Due to lags in compiling cause of death data in our databases, we will not have cause of death data in time for the study.

Death during hospitalization will also be assessed.

Laboratory-confirmed SARS-CoV-2 infection identified in the outpatient setting, without a hospitalization in the subsequent 14 days.

Exposures of interest: The exposure will be receipt of Pfizer's COVID-19 vaccine, with separate relative VEs estimated for those fully (2 dose), partially (1 dose), or ever vaccinated (≥1 dose) as in the TND design above. In this full cohort design, a patient's vaccination status, and thus exposure, will change over time, so VE will be estimated using time-varying exposures, explained in further detail below.

Partially and Fully Vaccinated: Partial (1 dose) and full (2 dose) vaccination VE will be estimated using time-varying exposures, with patients initially entering the cohort as unvaccinated, then contributing person time to the partial and fully vaccinated exposure groups as they are receiving the vaccine over time in the real-world setting. Specifically, a patient will move to the 1-dose exposure group once 14-days have passed following the first dose, and then to the 2-dose exposure group once 7-days have passed following the second dose. If a patient experiences an event within 14 days of the first dose, or 7 days within the second dose, he or she will be censored at that time. No requirements on the timing between doses will be applied.

To explore VE durability after 2 doses, secondary models will further refine the exposure categories to include time since receipt of dose 2. As in the main analysis, patients will still

enter the cohort as unvaccinated on 14 December 2020 (date of first vaccinations at KPSC) and will move from unexposed to the partial and full vaccinated exposure groups as they are vaccinated over time. Once the second dose is received, we will then code exposure categories as, for example, 1-29 days, 30-89 days, 90-180 days, 180-364, and ≥365 days since receipt of dose 2. Each patient will contribute person time to these groups as the allotted amount of time passes since their second dose. This will allow us to analyze the relative VE during those different time periods and explore VE durability. If sample size allows, we will conduct a similar analysis looking at only 1 dose, where patients will be censored from the analyses when they receive their second dose. To inform our decisions in choice of cut points for both dose models, we will also estimate changes in relative VE continuously over time by modeling time since vaccination using restricted cubic splines.

Ever Vaccinated: Relative VE for the Ever Vaccinated (≥1 dose) group will be estimated in a separate analysis also using time varying exposures. Patients will again enter the cohort as unvaccinated, then contributing person time to the ever-vaccinated group after receiving dose 1. They will remain in this exposure group regardless of receipt of the 2nd dose of the Pfizer COVID-19 vaccine.

Unexposed: Individuals with no record of BNT162b2 COVID-19 vaccination.

9.3.3. Test-Negative and Full Cohort Designs – Outside Vaccinations

To obtain information about vaccination that occurs outside of the KPSC healthcare system, we will also take advantage of the recent partnership KPSC established with 7 national pharmacy chains as well as data exchange with the California Immunization Registry (CAIR). This partnership allows for KPSC members to receive influenza and other vaccines outside of KPSC pharmacies. Starting 30 December 2020, a bidirectional data exchange was established with CAIR, thereby allowing us to capture vaccinations received outside of KPSC. CAIR bidirectionality brings together a partnership between electronic medical records, the public health department, and pharmacies. Doses administered outside of KPSC are currently being recorded in the electronic health record as, for example, “Covid-19 vaccine, Pfizer, external administration.”

One exception to this is that immunization data for San Diego patients is reported into the San Diego Immunization Registry (SDIR), not CAIR. Because SDIR does not currently provide data to CAIR, complete immunization information for San Diego patients is not yet available via KP HealthConnect. However, providers can do a manual query in SDIR to update member immunization records.

In California, COVID-19 vaccination providers are required to report COVID-19 doses administered within 24 hours of administration to their local immunization registry.

To verify our exposure data, we propose a validation study nested in the larger cohort study to survey a random sample of patients in the ‘non-vaccinated’ population to confirm data capture in the KPSC EHR (separate protocol).

9.3.4. Test-Negative and Full Cohort Designs - Covariates

We will consider individual-level and neighborhood-level factors listed in the Table 3 below. These are factors that we have either found to be important covariates in previous work, have been identified in other risk factor literature, or are variables that may be associated with the exposure as well as outcome (i.e. prior positive SARS-CoV-2 PCR test, etc.)[3-8]. We will also include calendar week as a covariate in our models to adjust for phase in vaccine rollout, testing practice changes, social distancing impacts, surges, and potential changes in clinical treatments.

Table 3. Factors to be considered in models

Demographics	Comorbidities	Care utilization prior to test	Neighborhood characteristics	COVID- history	Individual risk indicators
Age	Cardiac disease	Outpatient encounters	Population density	Prior negative PCR tests	Health care worker (HCW) / occupation
Sex	Organ transplant	Inpatient encounters	Median income	Prior positive PCR tests	Long-term care resident
Race/ethnicity	Diabetes with A1C	ED encounters	Neighborhood deprivation index	Prior negative serology tests	Medical Center
	Chronic Obstructive Pulmonary Disease (COPD)	Influenza vaccination	Education	Prior positive serology tests	
	Renal disease	Pneumococcal vaccination			
	Body mass index (BMI)				
	Malignancy				
	Hypertension				
	Charlson Index				
	Sedentary vs. Active				

9.4. Data sources

All data will be collected from KPSC electronic health records. This is a database analysis study of existing healthcare data; no patients will be actively enrolled. We will collect data including vaccination status and dates of vaccination, COVID-19 testing and outcomes, comorbidities, prior healthcare utilization, other vaccinations, demographic data, and other data from the EHR.

All data for research are subjected to a number of quality checks. The programming teams perform range and consistency checks for all data to be evaluated. These might include event dates after death, procedures coded at facilities that don't perform them, outlying laboratory values, and other evaluations. All study data are presented in team meetings on at least a weekly basis and further examinations for potential errors are made by the scientists and biostatisticians. In addition, at both sites there are a number of standard algorithms in place that will be used to further subject the data to quality control procedures. Aberrant data will be examined to determine if they are due to programming errors, and efforts to resolve systematic problems that lead to errors will occur as soon as possible after they are discovered and will continue until resolution. These quality control procedures will be documented, providing an auditable trail.

Once all necessary data from KPSC have been pulled and have undergone robust quality control measures, the databases will be frozen and archival copies of each separate dataset will be made. Continuous data quality assurance and improvement are a top priority. The team will be prompt in responding to any data quality inquiries from Pfizer if and when any issues are discovered.

All programming and analyses will be conducted using SAS statistical software, version 9·4 (Cary, NC), and R (R Core Team 2019, version 3.6.0).

9.5. Study size

The TND analysis will be event-driven based on the number of cases identified. Study sample size is based on the primary endpoint (BNT162b2 VE against ARI requiring hospitalization where SARS-CoV-2 is identified in the TND study). The required sample size will depend primarily on i) the proportion of all-cause ARI requiring hospitalization caused by SARS-CoV-2 (which determines the number of cases identified and the ratio of cases to controls in the primary analysis), ii) the average uptake of BNT162b2 in the study population over the duration of the study, and iii) the assumed VE of the specific COVID-19 vaccine against ARI requiring hospitalization where SARS-CoV-2 is identified. Sample size calculations were based on the following fixed assumptions:

Two-sided, type-I error of 5%

1. 90% power

2. Log(OR) following approximated normal distribution

3. Assumed true BNT162b2 VE varying from 70–90% to prevent ARI requiring hospitalization was modeled

4. 5% of all-cause ARI episodes requiring hospitalization will test positive for SARS-CoV-2. A range of 5–30% was also modeled given the attack rate of COVID-19 may vary based on social distancing and shelter-in-place measures, underlying levels of population immunity, and other factors.

Average BNT162b2 vaccine uptake in controls over the study period was allowed to vary in sample size calculations (range: 10–90%) and will depend on potential future vaccination uptake scenarios and timing of the conduct of the study. Final study enrollment size will also depend on the proportion of enrolled patients excluded from the Per Protocol Population because i) vaccination records could not be obtained, ii) they received a newly-licensed or investigational SARS-CoV-2 vaccine other than BNT162b2 vaccine, or iii) they received BNT162b2 vaccine, but did not receive the full 2-dose schedule.

Table 4 presents sample size calculations for various scenarios of BNT162b2 uptake and the proportion of all-cause ARI where SARS-CoV-2 is identified. Depending on the uptake of BNT162b2 and the proportion of ARI hospitalizations where SARS-CoV-2 is identified at the time of the study, approximately 3,000 to 12,000 persons ≥16 years of age will be needed in the TND analysis. Our study team will monitor BNT162b2 uptake among controls and the proportion of all-cause ARI where SARS-CoV-2 is identified to inform decisions on the sample size required to reach an effectiveness endpoint.

For the cohort design, analysis will be performed at fixed time points after a specified duration of follow-up. Power to detect a given hazard ratio in a Cox model depends primarily on the number of events observed during follow-up, but also varies with the degree of correlation between the exposure of interest (vaccination) and the other covariates in the model. Given that exposure at any given time may be highly correlated with age or comorbidities, we allowed the correlation (r^2) to vary from 0.1 to 0.5, while estimating a VE (1-HR) ranging from 30% to 90%. The power table below shows the total number of events which would need to be observed in the cohort to have 90% power at alpha level 0.05 to detect a given VE at a given correlation between vaccine exposure and other covariates.

Table 4. Total number of events needed to provide 90% power to detect a given VE

	Correlation of vaccine exposure with other covariates		
VE (1-HR)	**0.1**	**0.3**	**0.5**
90%	4	5	7
70%	13	17	23
50%	38	49	69
30%	144	185	259

Requirements for the final analysis population to detect BNT162b2 VE >20% assuming true VE=70–90% with 90% power and type-I error of 5% (2-sided) under various BNT162b2 uptake scenarios (5 to 30% of ARI events requiring hospitalization due to SARS-CoV-2)

Table 5. COVID VE Sample Size

	5% of ARI is SARS-CoV-2 positive				15% of ARI is SARS-CoV-2 positive				25% of ARI is SARS-CoV-2 positive				30% of ARI is SARS-CoV-2 positive			
Assume true VE=70%																
BNT162 Uptake	Con-trols	case s	Tot Eval	Tot En-roll*	Con-trols	case s	Tot Eval	Tot En-roll*	Con-trols	case s	Tot Eval	Tot En-roll*	Con-trols	case s	Tot Eval	Tot En-roll*
10	6769	356	7125	11875	2104	371	2475	4125	1171	390	1561	2602	938	402	1340	2233
20	3266	172	3438	5730	1022	180	1202	2003	573	191	764	1273	461	198	659	1098
30	2108	111	2219	3698	665	117	782	1303	377	126	503	838	304	130	434	723
40	1540	81	1621	2702	491	87	578	963	281	94	375	625	229	98	327	545
50	1213	64	1277	2128	392	69	461	768	228	76	304	507	187	80	267	445
60	1015	53	1068	1780	335	59	394	657	199	66	265	442	165	71	236	393
70	909	48	957	1595	308	54	362	603	187	62	249	415	157	67	224	373
80	905	48	953	1588	318	56	374	623	200	67	267	445	171	73	244	407
90	1174	62	1236	2060	435	77	512	853	287	96	383	638	251	108	359	598
Assume true VE=80%																
BNT162 Uptake	Con-trols	case s	Tot Eval	Tot En-roll*	Con-trols	case s	Tot Eval	Tot En-roll*	Con-trols	case s	Tot Eval	Tot En-roll*	Con-trols	case s	Tot Eval	Tot En-roll*
10	4945	260	5205	8675	1518	268	1786	2977	832	277	1109	1848	661	283	944	1573
20	2325	122	2447	4078	717	127	844	1407	396	132	528	880	315	135	450	750
30	1455	77	1532	2553	452	80	532	887	252	84	336	560	201	86	287	478
40	1024	54	1078	1797	321	57	378	630	181	60	241	402	146	63	209	348
50	770	41	811	1352	245	43	288	480	140	47	187	312	114	49	163	272
60	608	32	640	1067	197	35	232	387	115	38	153	255	95	41	136	227
70	505	27	532	887	169	30	199	332	102	34	136	227	85	36	121	202
80	455	24	479	798	160	28	188	313	101	34	135	225	86	37	123	205
90	513	27	540	900	196	35	231	385	132	44	176	293	116	50	166	277
Assume true VE=90%																

Table 5. COVID VE Sample Size

	5% of ARI is SARS-CoV-2 positive				15% of ARI is SARS-CoV-2 positive				25% of ARI is SARS-CoV-2 positive				30% of ARI is SARS-CoV-2 positive			
BNT162 Uptake	Con-trols	cases	Tot Eval	Tot En-roll*	Con-trols	cases	Tot Eval	Tot En-roll*	Con-trols	cases	Tot Eval	Tot En-roll*	Con-trols	cases	Tot Eval	Tot En-roll*
10	4275	225	4500	7500	1294	228	1522	2537	698	233	931	1552	549	235	784	1307
20	1955	103	2058	3430	594	105	699	1165	322	107	429	715	253	108	361	602
30	1183	62	1245	2075	361	64	425	708	197	66	263	438	155	66	221	368
40	798	42	840	1400	245	43	288	480	135	45	180	300	107	46	153	255
50	568	30	598	997	176	31	207	345	98	33	131	218	78	33	111	185
60	417	22	439	732	132	23	155	258	74	25	99	165	60	26	86	143
70	313	16	329	548	101	18	119	198	59	20	79	132	49	21	70	117
80	241	13	254	423	83	15	98	163	51	17	68	113	43	18	61	102
90	212	11	223	372	82	14	96	160	56	19	75	125	50	21	71	118

*Assumes 40% of enrolled participants will be unevaluable (i.e., excluded from the Per Protocol Population because i) vaccination records could not be obtained, ii) they received a newly-licensed or investigational SARS-CoV-2 vaccine other than COVID-19 vaccine, or iii) they received COVID-19 vaccine, but did not receive the full 2-dose schedule.

9.6. Data management

Data management activities include system operation and maintenance, security, data specification, programming, systems and data validation, sequencing of operational steps and events, quality assurance / quality control, and data backup.

The study team will hold weekly internal meetings with a primary goal surrounding quality assurance. The meetings will be a platform for the programmers and analysts to report their work in progress to the scientist team and to discuss any potential issues. KPSC will maintain internal data management logs to track data management activities and important communication with internal personnel or Pfizer.

In general, we will rely on our internal team meetings to manage tasks. Internal review processes and team meetings will be used to monitor performance. Meeting minutes, meeting agendas, progress reports, meetings, e-mail, and calendar tools will be used to manage and ensure quality of the project. We will use internal team meetings, e-mail, conference calls, the website, and progress reports to communicate. We will develop a document in coordination with the sponsor that will list all deliverables and expected timelines for deliverables. Tracking of project deliverables will be a standing item on meeting agendas.

Any problems or risks will be brought up at our regular internal team meetings and escalated to Pfizer as needed. The leadership team will discuss solutions to problems and ways to mitigate risks. We will use e-mail and our progress reports to communicate proactively with Pfizer regarding any anticipated risks or barriers to the project.

Once the study has begun, if Pfizer changes timelines or increases the scope of the objectives, we will examine all possible means to accommodate the changes within the existing budget. If not, we will work closely with Pfizer to adjust the budget, scope of work, and/or timelines.

9.6.1. Electronic data records

All data will be collected from KPSC electronic health records. This is a database analysis study of existing healthcare data; no patients will be actively enrolled. Therefore, no case report forms or data collection tools will be created and submitted to Pfizer. The investigator shall ensure that the electronic data records are securely stored at the study site and will have limited access. Patient-specific data will not be transferred or reported out to Pfizer. Aggregate descriptive analyses will be presented.

9.6.2. Record retention

The final database will be archived and retained in a password-protected location. To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, records, including the identity of all participating patients (sufficient information to link records, e.g., hospital records), source documents, detailed records of treatment disposition, and adequate docu-

mentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports) will be maintained. The records will be retained by the investigator according to site guidelines. The records will be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer will be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records will be kept for a minimum of 15 years after completion or discontinuation of the study. The investigator will obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.7.1. Test Negative Design Analyses

The analyses below will be done separately for the primary population of hospitalized patients as well as the secondary population of patients with ED encounters. Patients will be included in the analyses regardless of prior COVID-19 infection status.

9.7.1.1. Descriptive Analyses

We will give the proportion of hospitalized and ED patients with ARI where SARS-CoV-2 was identified, as well as the proportion of patients who receive 0, 1, and 2 doses of BNT162b2. We will provide the average and median time between receipt of the first and second dose of BNT162b2 among patients who received 2 doses, well as between 14 December 2020 (beginning of vaccinations at KPSC) and receipt of last dose of BNT162b2. Finally, we will describe age, gender, race/ethnicity, clinical characteristics, and severity (ICU admission, ventilator, death), and other characteristics described in Table 3 above of any patients who received BNT162b2 and test positive for SARS-CoV-2.

9.7.1.2. Estimated Crude (Unadjusted) VE

Odds of having received BNT162b2 (fully, ever, and partially vaccinated) for cases and test-negative controls will be constructed and compared using ORs and 95% confidence intervals (CIs). VE will be calculated as 1−OR multiplied by 100%. Corresponding 95% CIs will be calculated using the Wald method.

9.7.1.3. Estimating Adjusted VE

In addition to constructing crude OR and VE estimates, logistic regression modeling to assess BNT162b2 VE after adjustment for potentially confounding factors will be performed. With the exception of variables determined to be of clinical importance, which will be included in models regardless, variables described in 8.4.4 will be entered in the logistic regression model in backward stepwise manner. Only variables that change the estimated OR for BNT162b2 by ≥10% (i.e., confounder) will remain in the final VE model. A 2-sided alpha of .05 will be used for logistic regression modelling. Corresponding 95% CIs will be calculated using the Wald method. A generalized estimating equations (GEE) estimator will be used with a robust sandwich variance estimator to account for clustering introduced by variables measured at the neighborhood level. In addition to results from the final model, univariate VE results will be presented for each independent variable that is assessed for potential confounding, as the results from a fully-adjusted model.

9.7.1.4. Sensitivity Analyses

1. It is possible that patients that present with a COVID-19-like illness or a COVID-19 diagnosis are not tested for SARS-CoV-2 within 3 days of hospital admission but are rather tested later in their hospital stay. If this were the case, we would want to expand the requirement of a COVID-19 diagnostic test beyond 3 days following admission. To investigate the possibility of late testing, we will present data on the distribution of COVID-19 tests at time since admission for those admitted for respiratory infections. If we find that a meaningful number of patients are tested >3 days after hospital admission, we may include a sensitivity analysis to examine VE without time restrictions on testing following admission.

2. Use and develop Natural Language Processing (NLP) algorithm to estimate actual date of symptom onset of COVID-19 symptoms. Symptom onset will then be considered to define exposure status at the time of a qualifying event (or to censor a patient if they experience an event before 14-days after the first dose of 7-days after the second).

9.7.1.5. Exploratory analyses estimating VE for health care workers and other high risk populations

We know that the vaccine roll-out is following a tiered strategy, for example, with healthcare workers with direct patient contact being vaccinated first. The logic supporting tiered vaccine eligibility is based on COVID-19 risk, with highest risk populations prioritized first. To account for differing risk profiles of vaccinated individuals over time, we will account for calendar week in our model. To explore whether controlling for calendar week is sufficient to address possible biases in VE, we will explore three options:

1. Flag healthcare worker, or other sub-population status (gold standard).

This will require complete and reliable identification of healthcare worker or other sub-population status, for example, long term care facility (LTCF)-resident, in the EHR. This is the preferred approach.

Analyses will then be stratified so that both cases and controls will come from the same sub-population.

2. Explore and compare VE of models stratified by time periods.

KPSC documentation of the dates of transitions between tiers will be used to create categories of vaccine distribution by time (Healthcare works/LTCF residents only, 65+, etc.),

Using these categories, we will perform stratified analyses for each phase in the vaccine rollout and examine any differences in relative VE between time strata.

3. If, through our analyses in part 2 or as the result of additional clinical input, we determine our inability to identify patients eligible for vaccination during certain vaccination tiers will result in unobserved confounding that will materially affect the reliability of our VE estimates, we will limit VE analyses to certain time periods of interest for which we know vaccinations were restricted to a particular tier – in particular we may drop analyses focused on the time period only healthcare workers were vaccinated and focus on time periods were vaccination is more widespread.

Other Additional Analyses:

We will also perform the following analyses:

- Determine VE against hospitalization and ED admission (combined).
- Provide descriptive statistics and determine VE stratified by viral strains determined to be important or prevalent based on sequencing analyses.
- Determine VE of BNT162b2 against hospitalization stratified by various patient characteristics (e.g., age, sex, race/ethnicity, chronic medical conditions, pregnancy status, receipt of influenza vaccine). See Table 1 for full list of stratified analyses.
- Evaluate the effectiveness of BNT162b2 against severe hospitalization-related outcomes (e.g., ICU admission, mechanical ventilation, and death).
- Compare COVID-19 disease severity between vaccinated and unvaccinated cases.

We may also consider the impact of co-infections on analyses. It is possible that agents other than SARS-CoV-2 are the primary drivers causing ARI symptoms, while SARS-CoV-2 plays a less acute role. We may explore this possibility with descriptive analyses of the distribution of COVID-19 cases with diagnostic tests for other pathogens, and a sub-analysis excluding

all patients with co-infecting respiratory (influenza or Respiratory Syncytial Virus [RSV]) pathogens.

9.7.2. Full Cohort Design Analyses

As in the TND, we will include those with and without prior COVID-19 diagnoses.

9.7.2.1. Descriptive Analyses

We will give the proportion of patients who receive 0, 1, and 2 doses of BNT162b2 across all of KPSC during the study period. We will provide the average and median time between receipt of the first and second dose of BNT162b2 among patients who received 2 doses, as well as between 14 December 2020 (index date for cohort study, beginning of vaccinations at KPSC) and receipt of last dose of BNT162b2. Overall incidence of the outcomes of interest will be calculated by dividing the number of outcome cases by the total number of person-years. We will also provide incidence estimates by age, gender, race/ethnicity, clinical characteristics, and other characteristics described in Table 2 and Table 3 above. We will additionally explore changes in the clinical and demographic composition of the vaccinated and non-vaccinated population over time, as this will also change with vaccine phase integration. Characteristics of those who test positive for COVID-19 and those without COVID-19 will be presented.

9.7.2.2. Estimated Crude (Unadjusted) VE

VE will be estimated as 1 – [(incidence of outcome among vaccine recipients)/(incidence of outcome among unvaccinated)]. The incidence rate ratio will be estimated using the hazard ratio from the adjusted the Cox model, resulting in estimated VE = (1 – adjusted HR) * 100%. Corresponding 95% CIs will be calculated. Vaccination status will be time-varying as described previously in the Exposures section.

9.7.2.3. Estimating Adjusted VE

Adjusted hazard ratios (HRs) and 95% CIs will be estimated by including age, sex, race, and other covariates listed in Table 3 in Cox proportional hazards regression models. Covariates of clinical importance will be selected for the adjusted analyses. To determine whether the remaining covariates should be included in the final model, only variables that change the estimated HR for BNT162b2 by ≥10% (i.e., confounder) will remain in the final VE model. We will control for calendar week in all models. Robust variance will be computed to account for clustering introduced by neighborhood level variables. Vaccine effectiveness (VE) will be estimated as 1 – [(incidence of outcome among vaccine recipients)/(incidence of outcome among unvaccinated)]. The incidence rate ratio will be estimated using the hazard ratio from the adjusted the Cox model, resulting in estimated VE = (1 – adjusted HR) * 100%.

9.7.2.4. Sensitivity Analyses

Use and develop NLP algorithm to estimate actual date of symptom onset of COVID-19 symptoms. Symptom onset will then be considered to define exposure status at the time of a

qualifying event (or to censor a patient if they experience an event before 14-days after the first dose of 7-days after the second).

9.7.2.5. Exploratory analyses estimating VE for health care workers and other high risk populations

We know that the vaccine roll-out is following a tiered strategy, for example, with healthcare workers with direct patient contact being vaccinated first. The logic supporting tiered vaccine eligibility is based on COVID-19 risk, with highest risk populations prioritized first. To account for differing risk profiles of vaccinated individuals over time, we will account for calendar week in our model. To explore whether controlling for calendar week is sufficient to address possible biases in VE, we will explore three options:

- Flag healthcare worker, or other sub-population status (gold standard).
    - This will require complete and reliable identification of healthcare worker or other sub-population status, for example, LTCF resident, in the EHR. This is the preferred approach.
    - We will then include an interaction term with healthcare worker and HRs used to estimate VE, to determine if VE is meaningfully different by these categories.
- Explore and compare VE of models by time periods.
    - KPSC documentation of the dates of transitions between tiers will be used to create categories of vaccine distribution by time (Healthcare works/LTCF residents only, 65+, etc.),
    - Using these categories, we will perform stratified analyses for each phase in the vaccine rollout and examine any differences in relative VE between time strata.
- If, through our analyses in part 2 or as the result of additional clinical input, we determine our inability to identify patients eligible for vaccination during certain vaccination tiers will result in unobserved confounding that will materially affect the reliability of our VE estimates, we will limit VE analyses to certain time periods of interest for which we know vaccinations were restricted to a particular tier – in particular we may drop analyses focused on the time period only healthcare workers were vaccinated and focus on time periods were vaccination is more widespread.

9.7.3. Additional Analytic Elements for Test Negative and Full Cohort Design

<u>Other Analyses for Both Designs:</u>

- For cohort design, provide descriptive statistics and determine VE stratified by viral strains determined to be important or prevalent based on sequencing analyses.

- Determine VE of BNT162b2 stratified by various patient characteristics (e.g., age, sex, chronic medical conditions, receipt of influenza vaccine). Table 2 has the full list of proposed stratified analyses.

Laboratory Identification of Viral Strains

Residual nasopharyngeal or other respiratory specimens tested for COVID-19 as part of standard of care (SOC), will be collected daily from the two regional laboratories that serve the KPSC population. Specimens will be saved prior to being discarded for destruction. Swabs will be retained at the study site frozen until such time as they are selected and sent for variant determination which may include PCR and/or whole genome sequencing (WGS). WGS will occur for variants of interest, to identify circulating variants, and to assess VE against specific viral strains.

Missing or Incomplete Data:
Based on extensive prior experience, we expect negligible or no missing data for demographics, comorbidities, utilization, neighborhood characteristics (assessed through residential address data), COVID history, or societal-level factors. It is possible, however, that we will have missing data for occupation and LTCF variables. Regardless of missingness, we will present counts and percentages of missing data for all variables. If we find that data for variables included in the final models are highly complete, we will proceed with complete case analyses. If there is a substantial amount of missing data (>10%) for any variables deemed necessary to include in our final analyses, sensitivity analysis will be performed using multiple imputation for missing covariates (under the assumption of missing at random) to understand the impact of excluding patients with missing information in adjusted models.

Analysis Timings:
Prior to a final analysis, periodic interim analyses may be undertaken to understand attributes of emerging variants, to assess preliminary VE to respond to public health needs or to gauge sample size. Due to the observational nature of the study, no alpha adjustment will be applied. Any interim analyses will be described in the SAP.

9.8. Quality control

Data Quality Checks

Range checks and general frequency tables will be produced such that missing values, outliers, and inappropriate or abnormal values will be identified. Comparisons between date of birth, date of death, event dates and vaccination dates will be made. All data will be checked for duplicate records.

A record of data quality problems and resolutions will be kept through documented meeting minutes. All inconsistencies and/or data quality issues will be documented. Revisions will be noted in order to capture the change made, the change date, identification of the individual making the change, as well as noting any further actions to be taken to identify and/or resolve additional data quality problems of this type.

Select programming will be reviewed by a second programmer. A report will be created, listing discrepancies, their causes, and any action taken to resolve them. If there are discrepancies due to a difference in the date on which the original and validation programs are run, both programs may be run again on the same date as a means to eliminate this potential cause of discrepancies.

Confidentiality of Data

Any research data containing subject protected health information (PHI) is confidential. KPSC staff will not discuss research data with anyone other than KPSC personnel. Pfizer will only have access to aggregate data; no PHI will be shared with Pfizer.

9.9. Limitations of the research methods

If essentially all vaccine recipients receive two doses, we would be limited to studying the effect of 1 dose only during the time between doses, which could result in insufficient power to analyze the effectiveness of 1 dose. The ability to do certain stratified analyses listed above will also be limited by sample size and outcome rates in each of these groups.

Given the vaccine rollout to high-risk groups first and lower-risk groups later, the group who receives the vaccine initially may be significantly different from the comparison population. In particular, HCW vaccinated during this period would primarily be compared to non-HCW. While the rate of infection in HCW is largely driven by the rate of infection in the community 1, this discrepancy could result in a biased estimate. Any bias caused by HCW being higher risk than the general population will tend to bias the estimate toward lower VE. We will report E-values to quantify the impact of unmeasured confounding factors. The E-value is defined as the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the exposure and the outcome, conditional on the measured covariates, to fully explain away a specific exposure-outcome association. We will compare the E-value with covariate–outcome associations measured in concurrent literature (if available) that may have had data on HCW, employment status, or other unmeasured confounders and additionally compare the E-value with covariate–outcome associations among our measured covariates to determine if any association is likely to reach its magnitude. If we find it is not possible to overcome bias in early vaccine recipients using the TND or full cohort approach, we will exclude the early time period from analysis and begin the cohort at the time that a greater portion of the general public is able to receive the vaccine, resulting in a cohort start date when later batches of Pfizer vaccine are available.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data (PHI) in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by site and or/law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, , when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient consent

This is an observational database analysis study of existing healthcare data; no patients will be actively enrolled. As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required. The site will obtain a waiver for obtaining informed consent from the KPSC IRB.

10.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable or appropriate waiver for consent) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves electronic health record data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The Investigator will have primary responsibility for the expedient preparation, review and submission of any manuscripts, abstracts, press releases or other publications detailing the study's procedures or findings. The study team will follow the International Committee of Medical Journal Editors (ICMJE) criteria to determine authors, and all authors who meet these criteria will be offered authorship. We anticipate that as a collaborative project, members of each of the study organizations (KPSC and Pfizer) will participate. Each organization will determine members that meet authorship criteria. Any publication will include a list of investigators, with authors being determined in line with the ICMJE guidelines, as well as an acknowledgement of roles of the study Sponsor and Funder(s).

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

None

16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

17. ANNEX 2. ADDITIONAL INFORMATION

Appendix Table 1: Acute Respiratory Infection Diagnosis codes (International Classification of Diseases [ICD] codes)

ICD-10 code	ICD-10 definition
J12.0	Adenoviral pneumonia
J12.1	Respiratory syncytial virus pneumonia
J12.2	Parainfluenza virus pneumonia
J12.81	Pneumonia due to SARS-associated coronavirus
J12.3	Human metapneumovirus pneumonia
J12.89	Other viral pneumonia
J12.9	Viral pneumonia, unspecified
J13	Pneumonia due to Streptococcus pneumoniae
J18.1	Lobar pneumonia, unspecified organism
J15.0	Pneumonia due to Klebsiella pneumoniae
J15.1	Pneumonia due to Pseudomonas
J14	Pneumonia due to Hemophilus influenzae
J15.4	Pneumonia due to other streptococci
J15.4	Pneumonia due to other streptococci
J15.3	Pneumonia due to streptococcus, group B
J15.4	Pneumonia due to other streptococci

ICD-10 code	ICD-10 definition
J15.20	Pneumonia due to staphylococcus, unspecified
J15.211	Pneumonia due to Methicillin susceptible Staphylococcus aureus
J15.212	Pneumonia due to Methicillin resistant Staphylococcus aureus
J15.29	Pneumonia due to other staphylococcus
J15.8	Pneumonia due to other specified bacteria
J15.5	Pneumonia due to Escherichia coli
J15.6	Pneumonia due to other Gram-negative bacteria
A48.1	Legionnaires' disease
J15.8	Pneumonia due to other specified bacteria
J15.9	Unspecified bacterial pneumonia
J15.7	Pneumonia due to Mycoplasma pneumoniae
J16.0	Chlamydial pneumonia
J16.8	Pneumonia due to other specified infectious organisms
B25.0	Cytomegaloviral pneumonitis
A37.01	Whooping cough due to Bordetella pertussis with pneumonia
A37.11	Whooping cough due to Bordetella parapertussis with pneumonia
A37.81	Whooping cough due to other Bordetella species with pneumonia
A37.91	Whooping cough, unspecified species with pneumonia
A22.1	Pulmonary anthrax
B44.0	Invasive pulmonary aspergillosis
J17	Pneumonia in diseases classified elsewhere
B77.81	Ascariasis pneumonia
J17	Pneumonia in diseases classified elsewhere
J18.0	Bronchopneumonia, unspecified organism
J18.8	Other pneumonia, unspecified organism
J18.9	Pneumonia, unspecified organism
J10.00	Influenza due to other identified influenza virus with unspecified type of pneumonia
J10.01	Influenza due to other identified influenza virus with the same other identified influenza virus pneumonia
J10.08	Influenza due to other identified influenza virus with other specified pneumonia
J11.00	Influenza due to unidentified influenza virus with unspecified type of pneumonia
J11.08	Influenza due to unidentified influenza virus with specified pneumonia
J12.9	Viral pneumonia, unspecified
J10.1	Influenza due to other identified influenza virus with other respiratory manifestations
J11.1	Influenza due to unidentified influenza virus with other respiratory manifestations

ICD-10 code	ICD-10 definition
J10.2	Influenza due to other identified influenza virus with gastrointestinal manifestations
J10.81	Influenza due to other identified influenza virus with encephalopathy
J10.82	Influenza due to other identified influenza virus with myocarditis
J10.83	Influenza due to other identified influenza virus with otitis media
J10.89	Influenza due to other identified influenza virus with other manifestations
J11.2	Influenza due to unidentified influenza virus with gastrointestinal manifestations
J11.81	Influenza due to unidentified influenza virus with encephalopathy
J11.82	Influenza due to unidentified influenza virus with myocarditis
J11.83	Influenza due to unidentified influenza virus with otitis media
J11.89	Influenza due to unidentified influenza virus with other manifestations
J09.X1	Influenza due to identified novel influenza A virus with pneumonia
J09.X2	Influenza due to identified novel influenza A virus with other respiratory manifestations
J09.X3	Influenza due to identified novel influenza A virus with gastrointestinal manifestations
J09.X9	Influenza due to identified novel influenza A virus with other manifestations
J10.08	Influenza due to other identified influenza virus with other specified pneumonia
J10.1	Influenza due to other identified influenza virus with other respiratory manifestations
J09.X9	Influenza due to identified novel influenza A virus with other manifestations
J09.X1	Influenza due to identified novel influenza A virus with pneumonia
J09.X2	Influenza due to identified novel influenza A virus with other respiratory manifestations
J09.X3	Influenza due to identified novel influenza A virus with gastrointestinal manifestations
J09.X9	Influenza due to identified novel influenza A virus with other manifestations