

Estimating SARS-CoV-2 vaccine effectiveness among adults age 65 years and older using CMS data

Protocol Version: Dec 18, 2020



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Collaborators/Site Personnel

CDC

COVID-NET site co-investigators:

Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) is a population-based surveillance system that collects data on laboratory-confirmed COVID-19-associated hospitalizations among children and adults through a network of over 250 acute-care hospitals in 14 states: California, Colorado, Connecticut, Georgia, Iowa, Maryland, Michigan, Minnesota, New Mexico, New York, Ohio, Oregon, Tennessee, and Utah

Acumen

Background and summary of evaluation.

Adults ≥ 65 years of age (1,2) and residents in long-term care facilities (LTCFs) (3) are experiencing higher rates of hospitalizations due to COVID-19 disease compared to younger adults. Clinical trials evaluating SARS-CoV-2 vaccines are enrolling older adults; however, age group specific efficacy estimates may not be feasible to obtain through phase 3 studies. Older adults with comorbidities and LTCF residents have been identified as groups for early phases of vaccination against SARS-CoV-2 infection. It will be critical to evaluate post-introduction effectiveness of vaccines against SARS-CoV-2 among these groups at increased risk for disease and severe outcomes. CDC's COVID-19 vaccine effectiveness (VE) team is in planning stages for several post-introduction evaluations of effectiveness of SARS-CoV-2 vaccines.

CDC is proposing a case-control evaluation of effectiveness of SARS-CoV-2 vaccines against hospitalizations with COVID-19 disease among adults ≥ 65 years of age. Cases will be identified through COVID-NET, an ongoing population- and laboratory-based surveillance for COVID-19 disease conducted across 14 U.S. states. Records for COVID-19 case-patients who are also enrolled in Medicare part A/B will be linked to their Medicare part A/B claims data. The Medicare part A/B claims dataset will be used to select controls for cases, as well as obtain data on vaccination and medical history for cases and controls in order to estimate VE. CMS's Minimum Data Set (MDS) data will be used to identify beneficiaries among cases who are long-term care residents and to identify controls who are long-term care residents to estimate VE among LTCF dwelling adults ≥ 65 years of age. This evaluation will be carried out in collaboration with the CMS research contractor Acumen who will conduct the primary data analysis with technical assistance from CDC staff.

Objectives

- 1) Estimate post-introduction effectiveness of SARS-CoV-2 vaccines in preventing laboratory-confirmed COVID-19 hospitalizations among community dwelling adults ≥ 65 years of age.
- 2) Estimate post-introduction effectiveness of SARS-CoV-2 vaccines in preventing laboratory-confirmed COVID-19 hospitalizations among residents of long-term care facilities ≥ 65 years of age.

Methods

Design

A case-control design will be employed for this evaluation of effectiveness of SARS-CoV-2 vaccines against hospitalizations with COVID-19 disease among adults ≥ 65 years of age. Cases will be identified through COVID-NET, an ongoing population- and laboratory-based surveillance for COVID-19 disease conducted across 14 U.S. states. Case-patients who are also Medicare part A/B beneficiaries will be linked using select variables routinely collected through COVID-NET surveillance to their Medicare part A/B claims data. The Medicare part A/B claims dataset will be used to identify controls for each case. Data on vaccination and medical history, and other covariates necessary in order to estimate VE will also be obtained through Medicare part A/B claims. For the objective of evaluating SARS-CoV-2 VE along residents of long-term care facilities, CMS's Minimum Data Set (MDS) data will be used to identify beneficiaries among cases who are long-term care residents and to identify controls who are long-term care residents. Access to Medicare part A/B claims data and MDS data, and primary analysis will be carried out by the CMS research contractor Acumen, CDC will provide technical guidance during the analysis and interpretation of the data but will not have access to Medicare claims.

Population

The study population consists of residents in COVID-NET surveillance areas who are adults ≥ 65 years of age. COVID-NET comprises 99 counties in the 14 states participating in the Emerging Infections Program (EIP) and the Influenza Hospitalization Surveillance Project (IHSP). Participating states include California, Colorado, Connecticut, Georgia, Iowa, Maryland, Michigan, Minnesota, New Mexico, New York, Ohio, Oregon, Tennessee,

and Utah. COVID-NET covers approximately 10 percent of the U.S. population. The counties covered are in all 10 Health and Human Services (HHS) regions. The designated COVID-NET surveillance area is predominantly urban and may not be generalizable to the entire country.

Procedure

1) Vaccine effectiveness evaluation among community dwelling adults ≥ 65 years old:

Case identification

1. Cases will be identified through routine COVID-NET surveillance. COVID-NET cases are defined as a test positive for SARS-COV-2 in a surveillance area resident who was hospitalized within 14 days of the positive test. Information on demographics, date of hospital admission and laboratory results for positive SARS-CoV-2 test is collected for all cases (Appendix 1).
2. Acumen (with technical input from CDC collaborators) will develop an algorithm for matching COVID-NET cases in adults ≥ 65 years of age to Medicare part A/B records based on a set of variables routinely reported to CDC – date of birth, state, county, and zip code (or census tract) of residence, gender, race/ethnicity, date of hospitalization, date of positive test, and other variables as determined.

Control identification

1. Controls will be identified through Medicare part A/B claims data. Controls will be matched to cases on a set of characteristics, including but not limited to age group, length of enrollment in Medicare part A/B, Medicaid dual eligibility. The following options for control populations will be explored:
 - a. Test-negative controls: Medicare part A/B beneficiaries (age- and geographic-area matched) who have procedure codes for SARS-CoV-2 test with a recorded negative result. Feasibility of identifying test outcomes using available data sources will be explored.
 - b. Hospital-based controls: Medicare part A/B beneficiaries with hospitalizations within the defined time period (+/- 14 days) of corresponding case-patient's admission date, with non-COVID-19 diagnoses.
 - c. Population-based controls: Medicare part A/B beneficiaries without COVID-19-like illnesses residing in the same geographic area (zip code or census tract) as a case. All eligible controls identified within the matching category (i.e. within census tract and age group) will be included.

Data selection for cases and controls:

For cases successfully linked to Medicare part A/B beneficiaries and matched controls, the following information will be obtained through claims data:

- a) Medical history, including claims related to any diagnoses of chronic medical conditions known to be associated with an increased risk for development of COVID-19 disease
- b) Dates for SARS-CoV-2 vaccine doses received by type of vaccine (if more than one SARS-CoV-2 vaccine available)
- c) Dates for influenza vaccine doses received during the 2020-2021 season

Inclusion/exclusion criteria for cases and controls:

1. Inclusion criteria
 - a. COVID-19 cases ≥ 65 years old reported to COVID-NET
 - b. Cases matched to Medicare part A/B beneficiaries
 - c. Cases and controls with at least one continuous year of Medicare part A/B enrollment before the date of case-patient's hospitalization

2. Exclusion criteria

- a. Cases and controls with a Medicare part A/B record or COVID-NET data showing that they were a resident of a long-term care facility or long-term acute care facility in the 2 weeks prior to case date of hospitalization
- b. Cases with no matched eligible controls

2) Vaccine effectiveness evaluation among residents of long-term care facilities ≥ 65 years of age:

Same methods for case identification, control matching and claims data selection as for VE evaluation among community-dwelling adults will be employed.

- 1. Status of residence in long-term care facilities for all COVID-NET cases linked to their Medicare part A/B records will be ascertained from both part A/B claims and CMS’s Minimum Data Set (MDS).
- 2. Medicare part A/B beneficiaries without COVID-19 like illnesses who are residents of long-term care facilities will be included as controls and matched to cases on a set of characteristics that may include (but not limited to) age group, geographic area, and facility type.

Sample size and power

Sample size calculations were made using range of precision for VE estimates from 30% to 60%. We assumed a range of vaccine coverage among controls (30 to 70%) and vaccine effectiveness ranging from 30% to 90%. Assuming coverage of 30% among controls, a VE of 30%, with VE estimate precision of 30%, 613 cases and 1839 controls with 1:3 case:control ratio will be needed. As the vaccine coverage increases, the number of cases required to demonstrate target effectiveness decreases (Table 1).

Table 1: Sample size estimates using ranges of vaccine effectiveness (VE) precision, vaccine coverage, and 3:1 control to case ratio

VE	Precision	Vaccine Coverage	Control to case ratio	No. of cases	No. of controls
30%	30%	30%	3	613	1839
30%	30%	50%	3	464	1392
30%	30%	70%	3	495	1485
30%	60%	30%	3	160	480
30%	60%	50%	3	121	363
30%	60%	70%	3	129	387
60%	30%	30%	3	274	822
60%	30%	50%	3	178	534
60%	30%	70%	3	160	480
60%	60%	30%	3	77	231
60%	60%	50%	3	50	150
60%	60%	70%	3	45	135
70%	30%	30%	3	191	573
70%	30%	50%	3	116	348
70%	30%	70%	3	95	285
70%	60%	30%	3	57	171
70%	60%	50%	3	34	102
70%	60%	70%	3	28	84

80%	30%	30%	3	123	369
80%	30%	50%	3	68	204
80%	30%	70%	3	50	150
80%	60%	30%	3	41	123
80%	60%	50%	3	23	69
80%	60%	70%	3	17	51
90%	30%	30%	3	73	219
90%	30%	50%	3	36	108
90%	30%	70%	3	22	66
90%	60%	30%	3	31	93
90%	60%	50%	3	16	48
90%	60%	70%	3	9	27

Data management and quality assurance

Data Use Agreement between CDC and Acumen (CMS contractor) will be established; CDC will share line lists of COVID-19 cases identified through COVID-NET with limited set of variables to help with linkage including: date of birth, state, county, zip code, gender, race/ethnicity, date of hospitalization, date of positive SARS-CoV-2 test, and any other variables as determined. These line lists will be shared with Acumen through a secure share point site. COVID-NET sites will not directly share any data with Acumen and no data use agreements between the COVID-NET sites and Acumen will be established.

Acumen will conduct matching using algorithm developed with CDC input, and share summaries of data analysis, including proportion of case and control with SARS-CoV-2 vaccine claims, proportion of cases and controls with chronic medical conditions. The primary analysis evaluating SARS-COV-2 vaccine effectiveness will be conducted with technical input and guidance from CDC. Summaries with analyses will be shared with CDC and COVID-NET staff using secure data transfer portal.

CDC will hold weekly calls with Acumen to conduct analysis and generate summaries. Analytic plan will be developed in collaboration with COVID-NET investigators and Acumen staff.

Data analysis

Data will be aggregated and analyzed by Acumen following the analytic plan developed by CDC in collaboration with COVID-NET and Acumen investigators. The analyses will include evaluating feasibility of selecting different control groups using claims data (test-negative, hospital-based, and population based). Characteristics of cases and controls will be compared using chi-square tests or Fisher's exact tests (for categorical variables) or Wilcoxon rank-sum tests (for continuous variables).

Vaccine effectiveness will be estimated using conditional logistic regression as:

$$\text{Vaccine effectiveness} = (1 - \text{matched, adjusted odds ratio for vaccination}) \times 100\%$$

We will adjust for potential confounders in all analyses. If population-based control group is selected for VE analysis, we will evaluate use of propensity scores (weighting) or utility of instrumental variable methods to minimize bias due to factors related to health seeking behaviors (including vaccine receipt). Vaccine doses received within 14 days before case-patient's hospitalization date will be excluded from the analysis.

The primary analysis will evaluate the effectiveness of 2 doses of SARS-CoV-2 vaccine vs. no SARS-CoV-2 vaccine. A secondary analysis will evaluate the effectiveness of any SARS-CoV-2 vaccine doses vs. no SARS-CoV-2 vaccine, or one dose vs. no vaccine. More than one SARS-CoV-2 vaccine may be available during early

phases of vaccine introduction among HCPs. If there are multiple vaccines, VE analysis will be stratified by vaccine type.

Human Subjects Review

This vaccine effectiveness evaluation is designed to evaluate the effects of post-introduction SARS-CoV-2 vaccine(s). This evaluation involves secondary analysis of surveillance data routinely collected at CDC and linked to Medicare part A/B data. There is no more than minimal risk to the study participants as there will be no interventions or modifications to the care subjects receive. COVID-NET data used are collected as part of routine COVID-19 surveillance. Medicare part A/B claims data are generated as part of routine care. CDC personnel will not have access to Medicare part A/B primary data and the analysis will be performed by Acumen (CMS research contractor). Only summary data will be transmitted by Acumen to CDC via secure site. This protocol will be submitted for IRB determination and clearance by CDC and COVID-NET site institutions.

Funding

US CDC

Timelines

December 20, 2020: Protocol finalized and submitted to CDC's National Center for Immunization and Respiratory Diseases (NCIRD) human subjects advisor

January 1 – January 31: Pilot work to develop algorithm to link COVID-Net cases and CMS beneficiaries, explore possibilities for appropriate control selection

January 1, 2021 – June 1, 2021 (or longer, depending on the timelines for vaccine introduction and uptake in the target population): Analyze vaccine coverage data, identify dataset for VE evaluation, VE analysis, report initial findings

Note: Exact timing of the final analysis will depend on how rapid the vaccine update is in population of interest.

References

1. Garg S, Kim L, Whitaker M, et al. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 — COVID-NET, 14 States, March 1–30, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:458–464. DOI: <http://dx.doi.org/10.15585/mmwr.mm6915e3external icon>.
2. Wortham JM, Lee JT, Althomsons S, et al. Characteristics of Persons Who Died with COVID-19 — United States, February 12–May 18, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:923–929. DOI: <http://dx.doi.org/10.15585/mmwr.mm6928e1external icon>.

3. McMichael TM, Clark S, Pogosjans S, et al. COVID-19 in a Long-Term Care Facility — King County, Washington, February 27–March 9, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:339-342. DOI: <http://dx.doi.org/10.15585/mmwr.mm6912e1external icon>.

Appendix 1: Sections of COVID-NET case report form completed for all identified cases

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL
AND PREVENTION
ATLANTA, GA 30329

**COVID-19-Associated Hospitalization Surveillance
Case Report Form**



Case ID: <u>C 2 0 2 1</u>		CDC 2019-nCoV ID: _____		NNDSS loc. rec. ID/Case ID: _____	
A. Patient Data – THIS INFORMATION IS NOT SENT TO CDC					
Last Name:		First Name:		Middle Name:	Chart Number:
Address:				Address Type:	
City:		State:		Zip Code:	
Site Use:					CDCTrack: _____
B. Abstractor Information – THIS INFORMATION IS NOT SENT TO CDC					
1. Abstractor Name:			2. Date of Abstraction: ____/____/____		
C. Enrollment Information					
1. Admission Type: <input type="checkbox"/> Hospitalization <input type="checkbox"/> Observation only	2. State:	3. County:		4. Case Type: <input type="checkbox"/> Pediatric <input type="checkbox"/> Adult	5. Date of Birth: ____/____/____
6. Age: _____ <input type="checkbox"/> Years <input type="checkbox"/> Months (if < 1 yr) <input type="checkbox"/> Days (if < 1 month)	7. Sex: <input type="checkbox"/> Male <input type="checkbox"/> Female				
8. Race: <input type="checkbox"/> White <input type="checkbox"/> Black or African American <input type="checkbox"/> Asian/Pacific Islander <input type="checkbox"/> American Indian or Alaska Native <input type="checkbox"/> Multiracial <input type="checkbox"/> Not specified		9. Ethnicity <input type="checkbox"/> Hispanic or Latino <input type="checkbox"/> Non-Hispanic/Latino <input type="checkbox"/> Not Specified		10. Type of Insurance (select all that apply): <input type="checkbox"/> Private <input type="checkbox"/> Medicare <input type="checkbox"/> Medicaid/state assistance program <input type="checkbox"/> Military <input type="checkbox"/> Indian Health Service <input type="checkbox"/> Incarcerated <input type="checkbox"/> Uninsured <input type="checkbox"/> Unknown <input type="checkbox"/> Other, specify: _____	
11. Pregnant? (15-49 years of age only): <input type="checkbox"/> Yes <input type="checkbox"/> No/Unknown <input type="checkbox"/> Not applicable (male)			12. Hospital ID Where Patient Treated: _____ 12a. Admission Date: ____/____/____ 12b. Discharge Date: ____/____/____		
13. Was patient transferred from another hospital? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown		13a. Transfer Hospital ID: _____		13b. Transfer Hospital Admission Date: ____/____/____ 13c. Transfer Date: ____/____/____	
14. Where did patient reside at the time of hospitalization: <input type="checkbox"/> Private residence <input type="checkbox"/> Hospice <input type="checkbox"/> Homeless/shelter <input type="checkbox"/> Hospitalized since birth <input type="checkbox"/> Unknown <input type="checkbox"/> Home with services <input type="checkbox"/> Facility <input type="checkbox"/> Corrections facility <input type="checkbox"/> Other, specify: _____					
D. SARS-CoV-2 Testing Results (can add up to 10 test results in database)					
1. Test 1: <input type="checkbox"/> Molecular Assay (e.g. RT-PCR, RVP) <input type="checkbox"/> Serology <input type="checkbox"/> Method Unknown <input type="checkbox"/> Other, specify: _____					
1a. Specimen collection date: ____/____/____		1b. Specimen collection ID: _____		1c. Testing facility ID: _____	
1d. Test result: <input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Indeterminate					
2. Test 2: <input type="checkbox"/> Molecular Assay (e.g. RT-PCR, RVP) <input type="checkbox"/> Serology <input type="checkbox"/> Method Unknown <input type="checkbox"/> Other, specify: _____					
2a. Specimen collection date: ____/____/____		2b. Specimen collection ID: _____		2c. Testing facility ID: _____	
2d. Test result: <input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Indeterminate					