Emulating target trials using VA EHR data: an application to the comparative effectiveness of mRNA-based Covid-19 vaccines

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Disclosures

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  - Disclaimer: The contents of this presentation reflect the views of the authors and not necessarily the position of the VA or U.S. Government.
- The VA-CAUSAL Methods Core is a collaboration between the Massachusetts Veterans Epidemiology, Research, and Information Center (MAVERIC) Division of Population Health and Data Sciences and the CAUSALab at the Harvard T.H. Chan School of Public Health.

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Comparative Effectiveness of BNT162b2 and mRNA-1273 Vaccines in U.S. Veterans

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Article

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Comparative effectiveness of third doses of mRNA-based COVID-19 vaccines in US veterans

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Comparative effectiveness of third doses of BNT162b2 (Pfizer-BioNTech) vs. mRNA-1273 (Moderna) vaccines

- **Third doses of mRNA-based vaccines have provided a way to address waning immunity and broaden protection against emerging SARS-CoV-2 variants**
  - But evidence was lacking for their comparative effectiveness for a range of Covid-19 outcomes across diverse populations
- **We used the VA healthcare databases to emulate a target trial and generate this evidence**
  - In the overall population, and in subgroups defined by age, race, time since completion of primary vaccination series, vaccine type of primary series
  - In time periods spanning SARS-CoV-2 delta- and omicron-variant predominance, and restricted to omicron-variant predominance

Protocol of a target trial of third doses of BNT162b2 vs. mRNA-1273 vaccines and risk of Covid-19 outcomes

Eligibility criteria	Veterans aged ≥65 years or 18-64 years with high risk of severe Covid-19 between October 20 and November 18, 2021, or ≥18 years between November 19, 2021, and February 8, 2022 (based on national guidelines for third dose deployment); receipt of the second dose of an mRNA vaccine primary series at least 6 months earlier (based on the same guidelines); known residential address outside of a long-term care facility, use of the VA healthcare system during the past year but not in the past 3 days, known smoking status and BMI in the past year...
Treatment strategies	1. Third dose of BNT162b2 vaccine at baseline 2. Third dose of mRNA-1273 vaccine at baseline
Assignment procedures	Participants are randomly assigned to a strategy at baseline within strata defined by calendar date of third dose, calendar month of second mRNA vaccine dose, age, sex, race, urbanicity of residence, geographic location, number of SARS-CoV-2 tests performed in the past 12 months
Outcomes	(1) Documented SARS-CoV-2 infection, (2) Symptomatic Covid-19, (3) Covid-19 hospitalization, (4) Covid-19 ICU admission, (5) Covid-19 death
Follow-up	Starts on the day of third dose receipt (baseline) and ends on the day of the outcome of interest, death, 112 days (16 weeks) after baseline, or the end of the study period (February 15, 2022)
Causal contrast	Per-protocol effect
Analysis plan	Cumulative incidence (risk) curves comparing the vaccination groups. Subgroup analyses by baseline age, race, time since completion of primary series, vaccine type of primary series

Evaluating the influence of SARS-CoV-2 variants on vaccine comparative effectiveness

- Period spanning delta- and omicron-variant predominance
  - Target trial described
- Period restricted to omicron-variant predominance
  - A second identical target trial, except
    - Recruitment: January 1 to March 1, 2022
    - Only outcome is documented infection

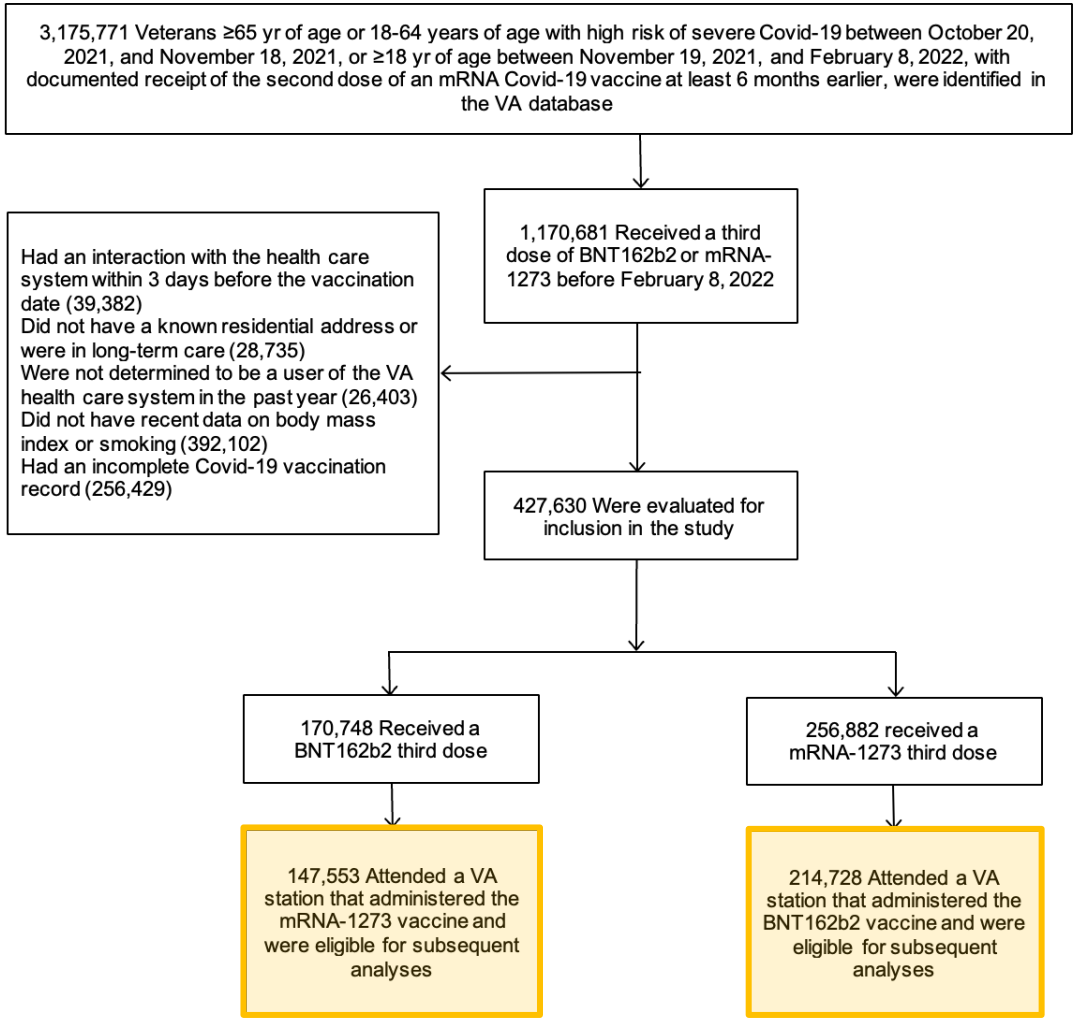
We emulated these target trials using a national database of electronic health records

- **U.S. Department of Veterans Affairs (VA) healthcare system**
  - Largest integrated healthcare system in the U.S.
- **VA Corporate Data Warehouse (CDW)**
  - Detailed information on demographics, inpatient and outpatient encounters, medications, laboratory results
  - Data refreshed nightly
  - Decades of follow-up

Mapping variables to the available data

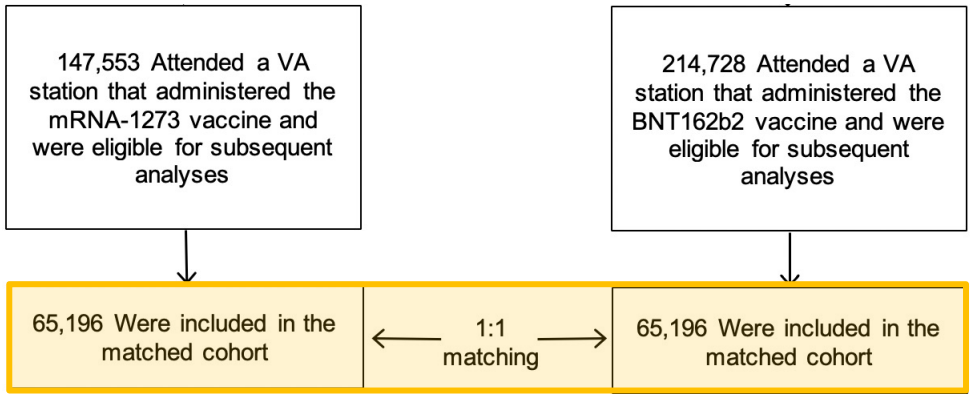
Variable	Ascertainment
Covid-19 vaccination	Records in *Immunization* domain and procedures recorded in *Outpatient* or *Inpatient* domains
SARS-CoV-2 infection	VA Covid-19 National Surveillance Tool
Symptomatic Covid-19 (≥1 symptoms documented within 4 days of infection: fever, chills, cough, shortness of breath/difficulty breathing, sore throat, loss of taste/smell, headache, myalgia/muscle pain, diarrhea, vomiting)	Records in *Outpatient*, *Inpatient*, *Vital Signs*, *Health Factors*, and *Fee* domains
Covid-19 related hospitalization (a hospitalization within 21 days of infection)	Records in *Inpatient* domain
Covid-19 related ICU admission (an ICU admission during a Covid-19 hospitalization)	Records in *Inpatient* domain and specialty transfer codes
Covid-19 death (a death within 30 days of SARS-CoV-2 infection)	Records in *Patient* domain

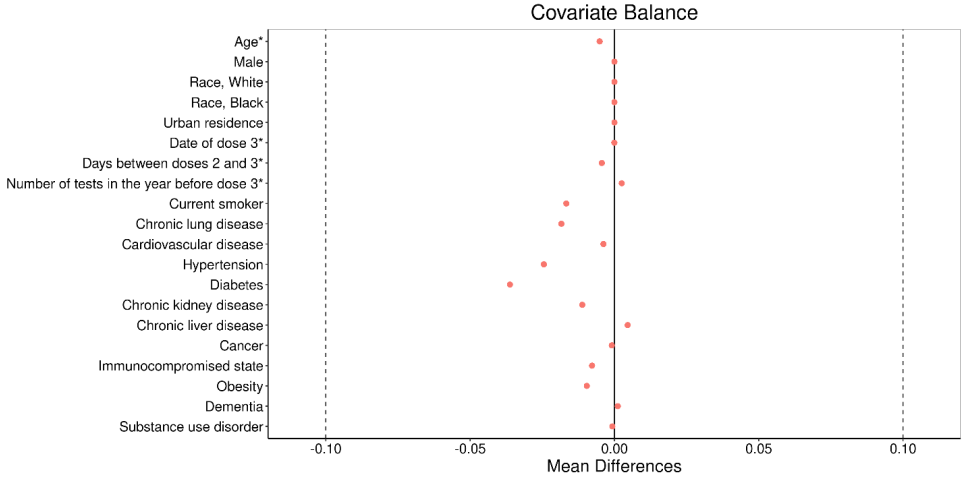
Applied the same eligibility criteria to Veterans in the database



Closely matched recipients of each vaccine

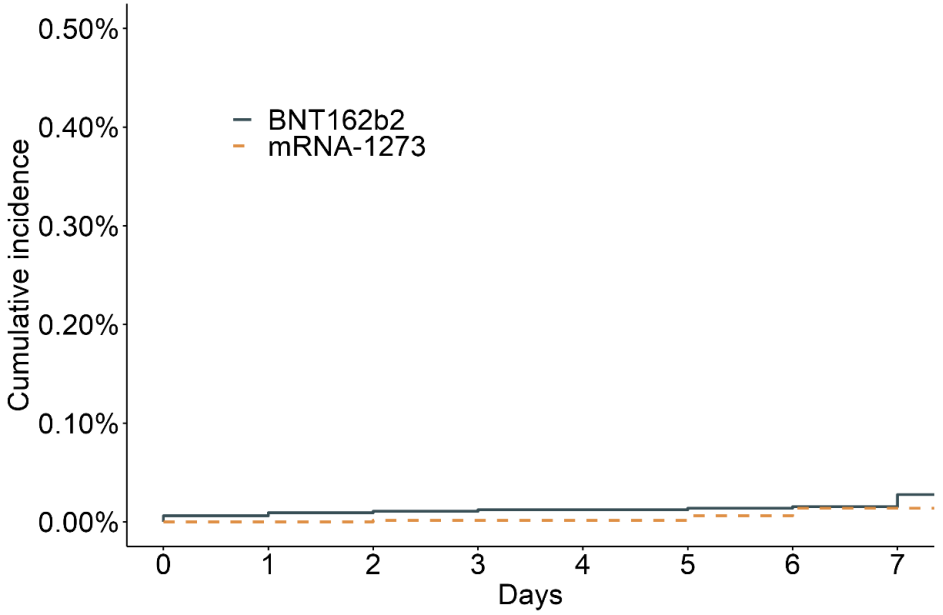
- Based on risk factors for infection or Covid-19 severity also associated with the probability of receiving a particular vaccine
  - Calendar date of third dose, calendar month of second mRNA vaccine dose, age, sex, race, urbanicity of residence, geographic location, number of SARS-CoV-2 tests performed in the past 12 months
- All measured variables were well-balanced between the 2 groups



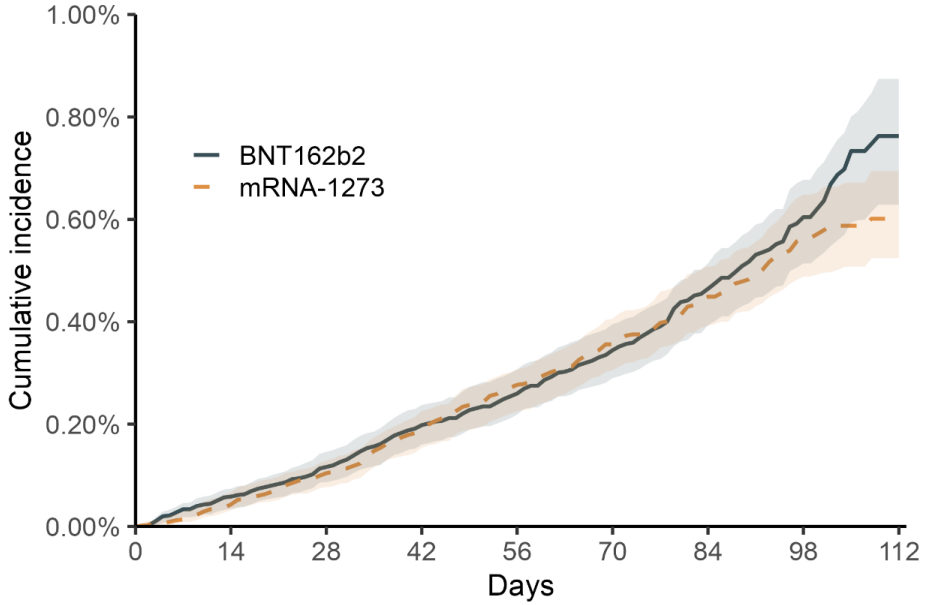


Negative control analyses suggested little confounding

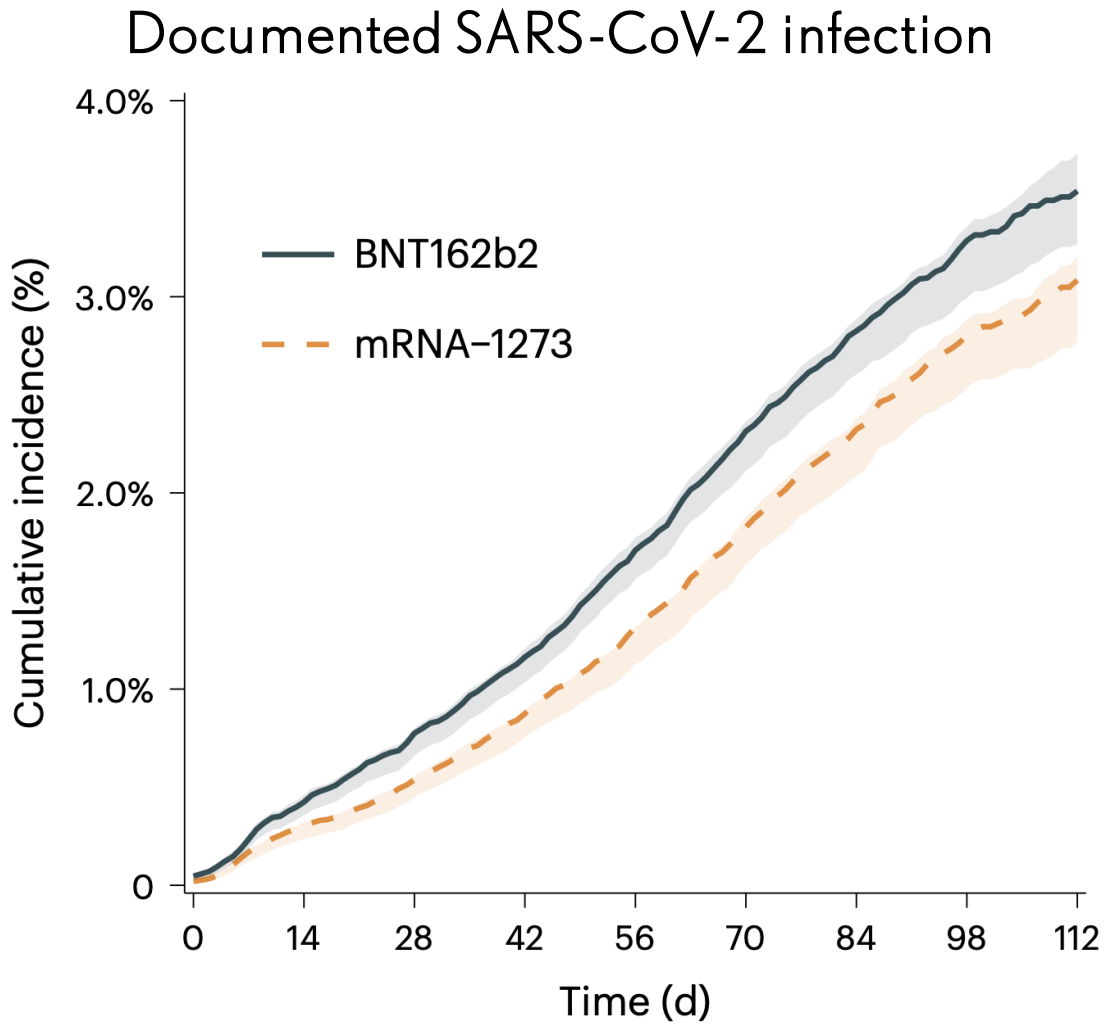
Negative control outcome #1:
Symptomatic Covid-19 in the first 7 days after the third vaccine dose



Negative control outcome #2:
Non-Covid-19 death over the follow-up



Slightly lower risk of all studied Covid-19 outcomes for a third dose of the mRNA-1273 vs. BNT162b2 vaccine



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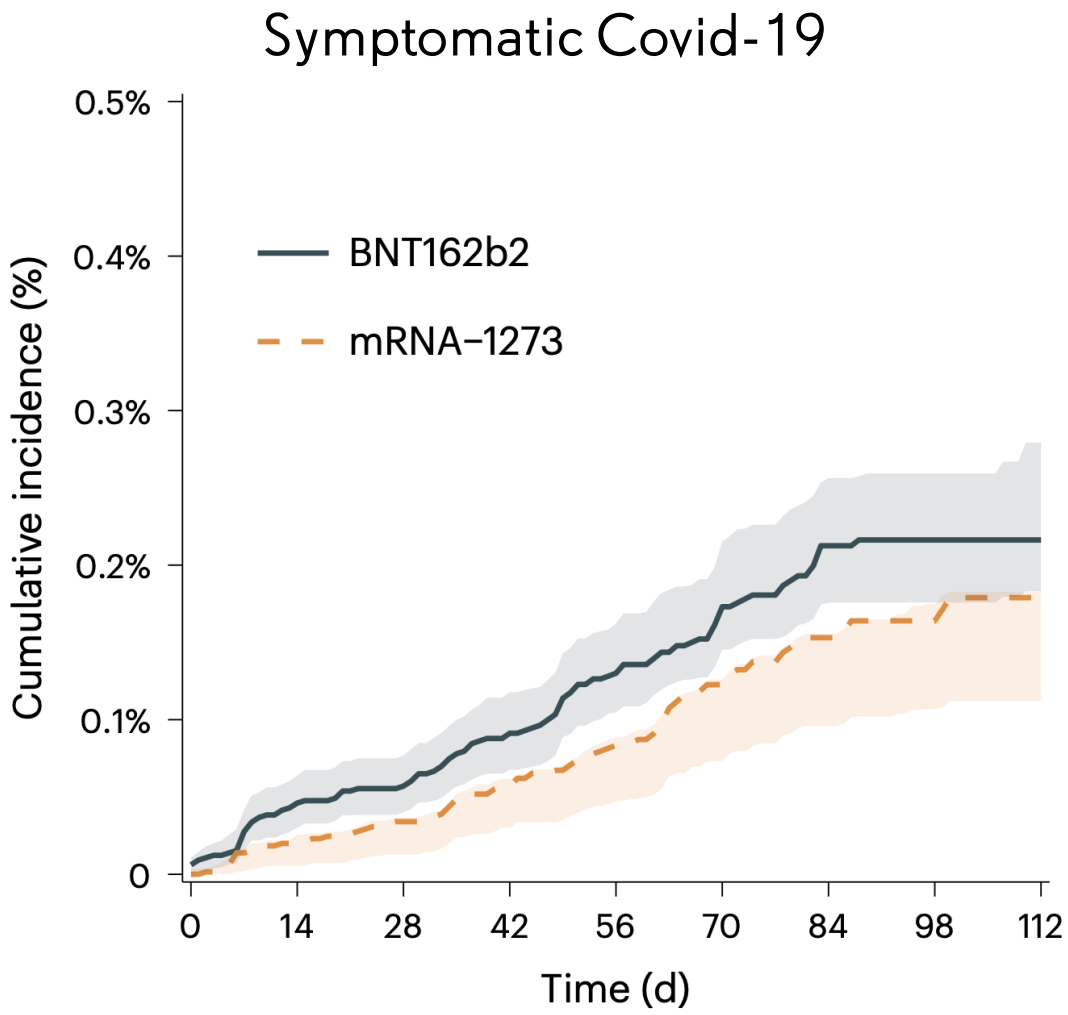

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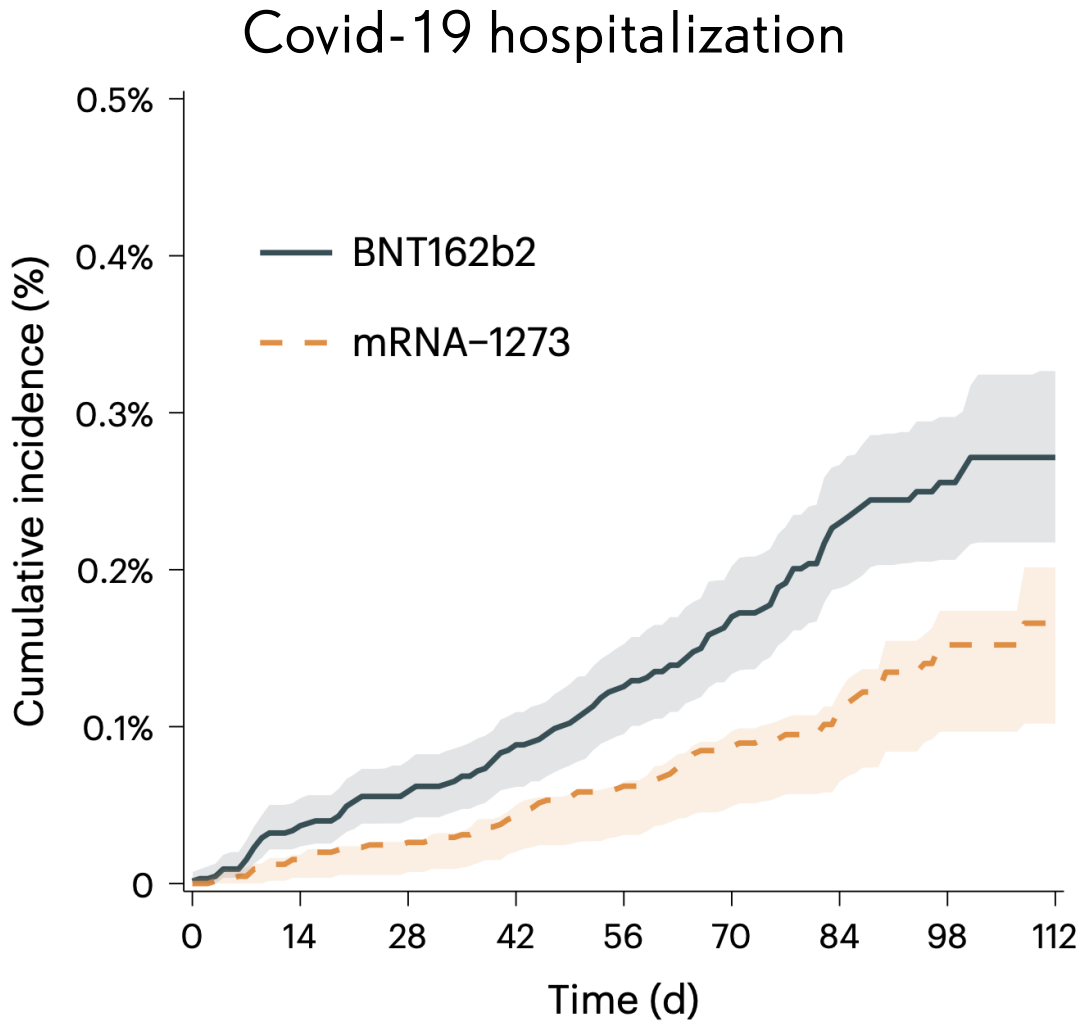

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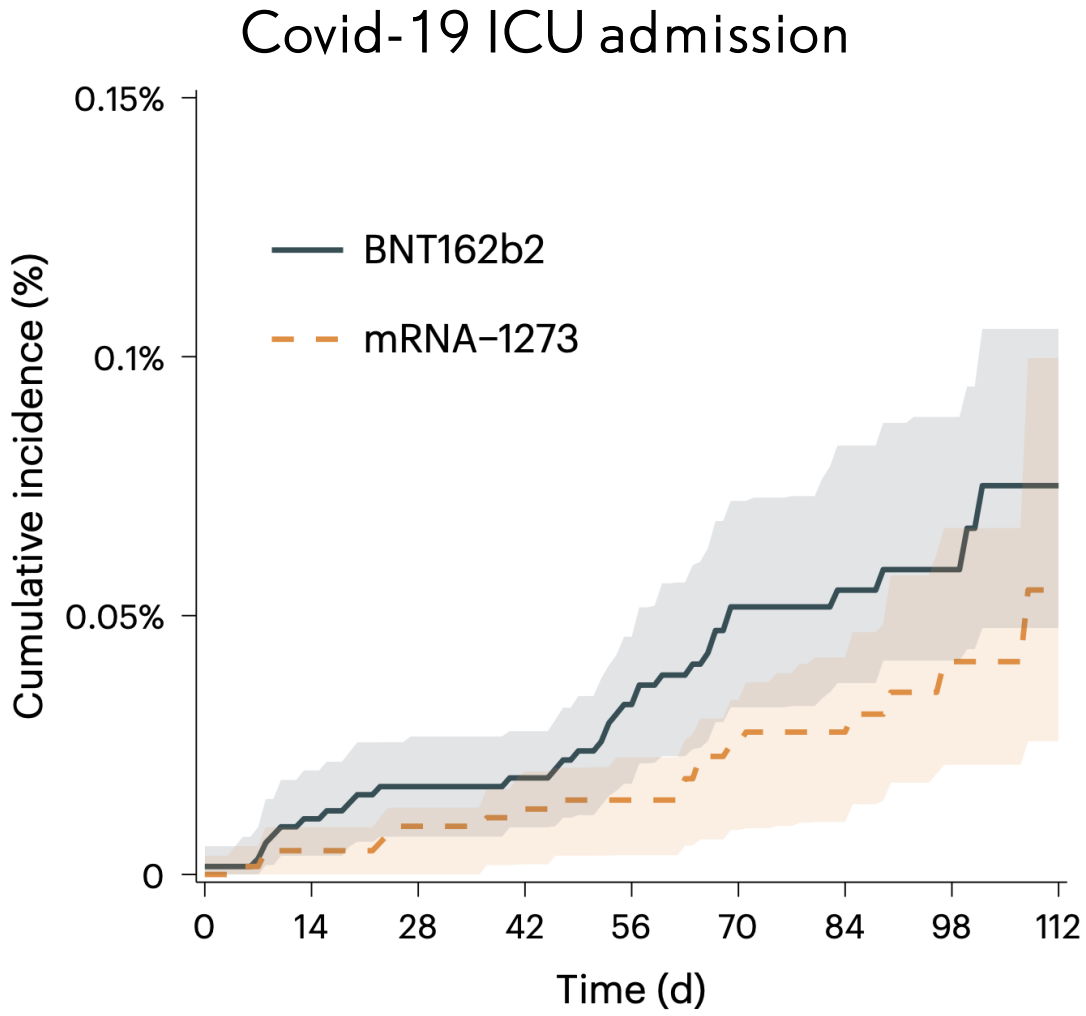

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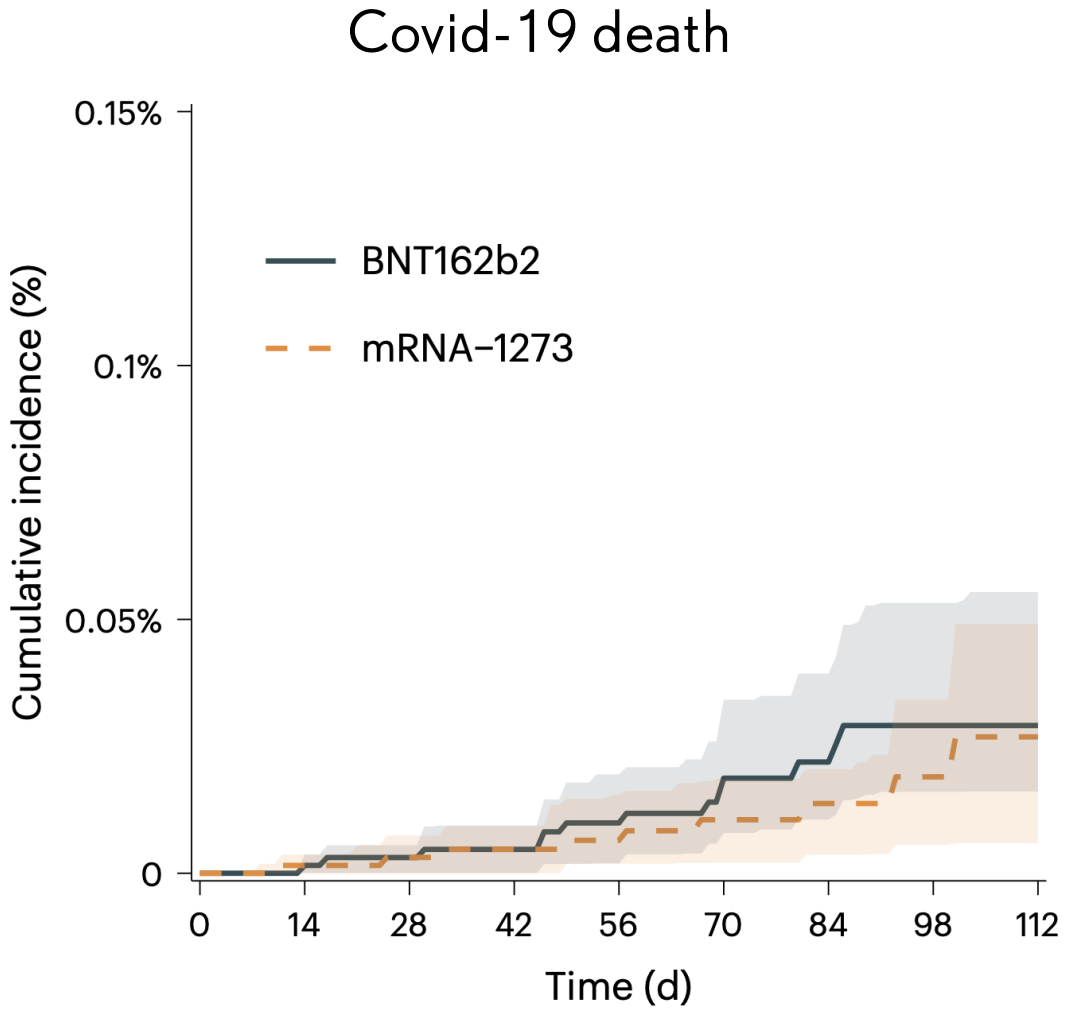
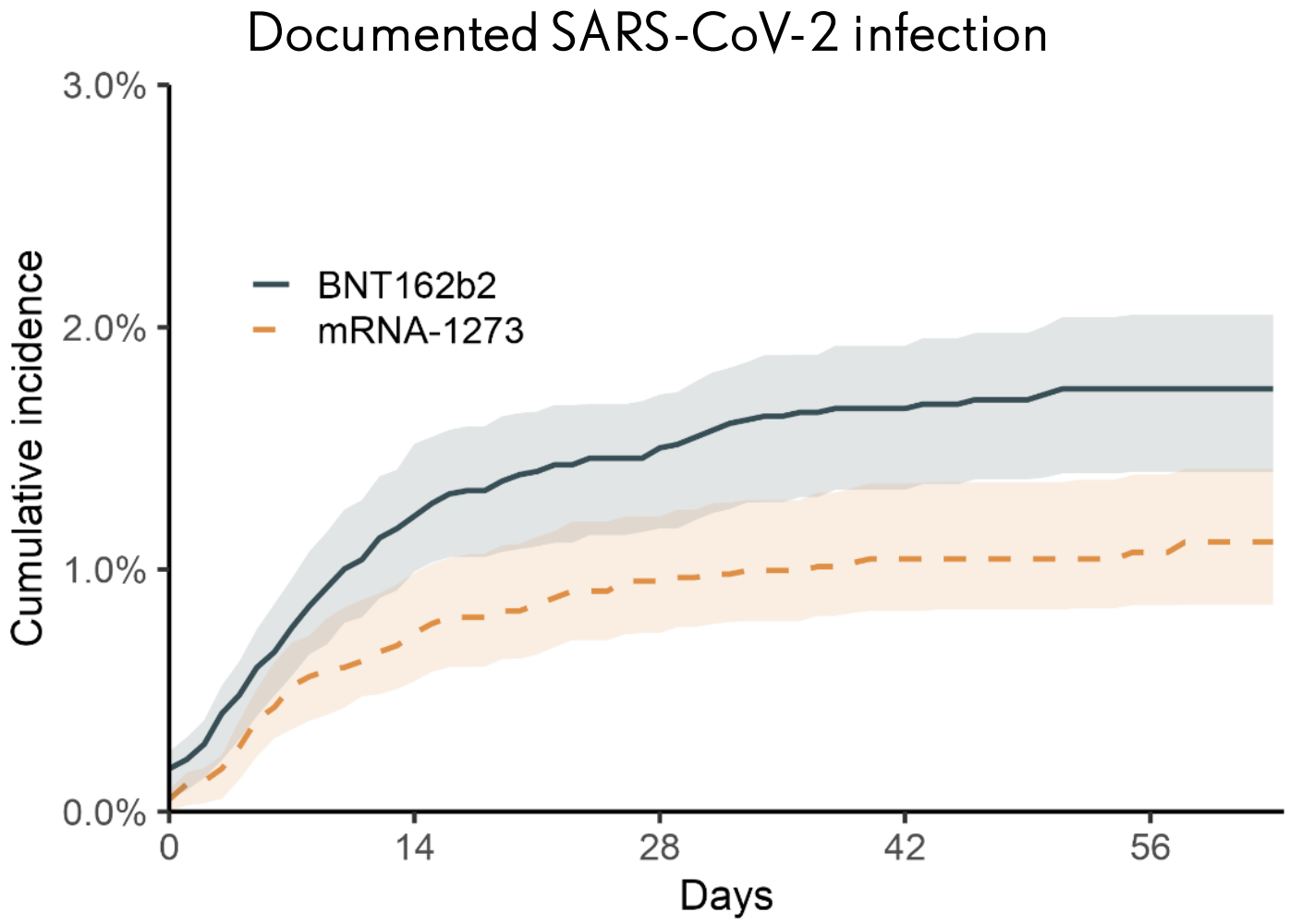


This pattern was similar in a time period restricted to omicron-variant predominance



Key Takeaways

- Absolute risks of the studied Covid-19 outcomes over 16 weeks were low regardless of the third mRNA vaccine received, during a period spanning delta- and omicron-variant predominance
  - Risks <4% for infection, <0.03% for death, within each vaccine group
- Evidence for a lower risk of Covid-19 outcomes for the mRNA-1273 vs. BNT162b2 vaccine over the study period
  - 45 fewer infections, 11 fewer hospitalizations per 10,000 persons
- Similar pattern for documented infection over 9 weeks during a period restricted to omicron-variant predominance

Methodologic Takeaways

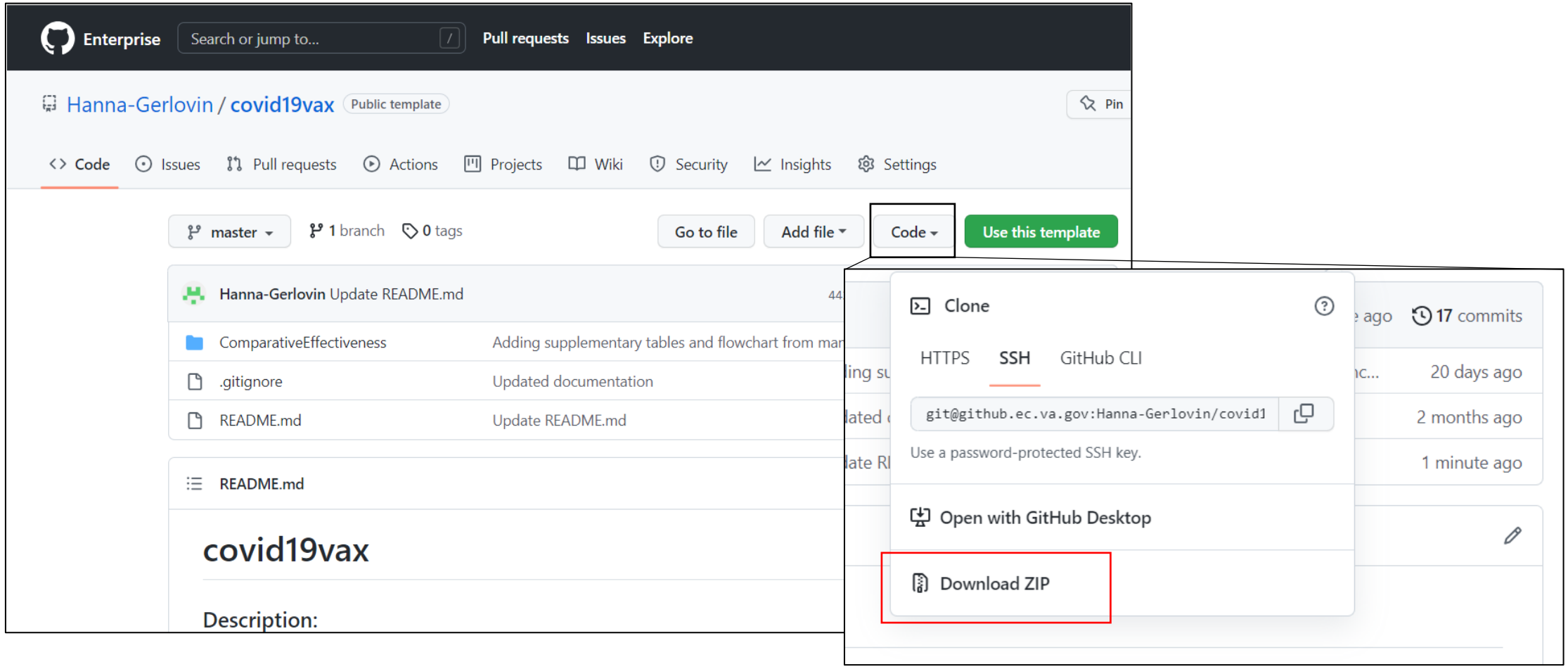
- It is possible to design and conduct a rapid response study using sound causal techniques and VA EHR data
  - Leveraging existing resources for Covid-19 data
  - Incorporating best practices for phenotyping and utilization of computational resources
- Standardized elements can assist with study design
  - Target trial protocol specification and emulation table
  - Flowchart for the selection of eligible individuals
- Analytic programs streamlined for flexibility
  - Parameterizing the analysis process to handle multiple sensitivity analyses

Sharing Materials

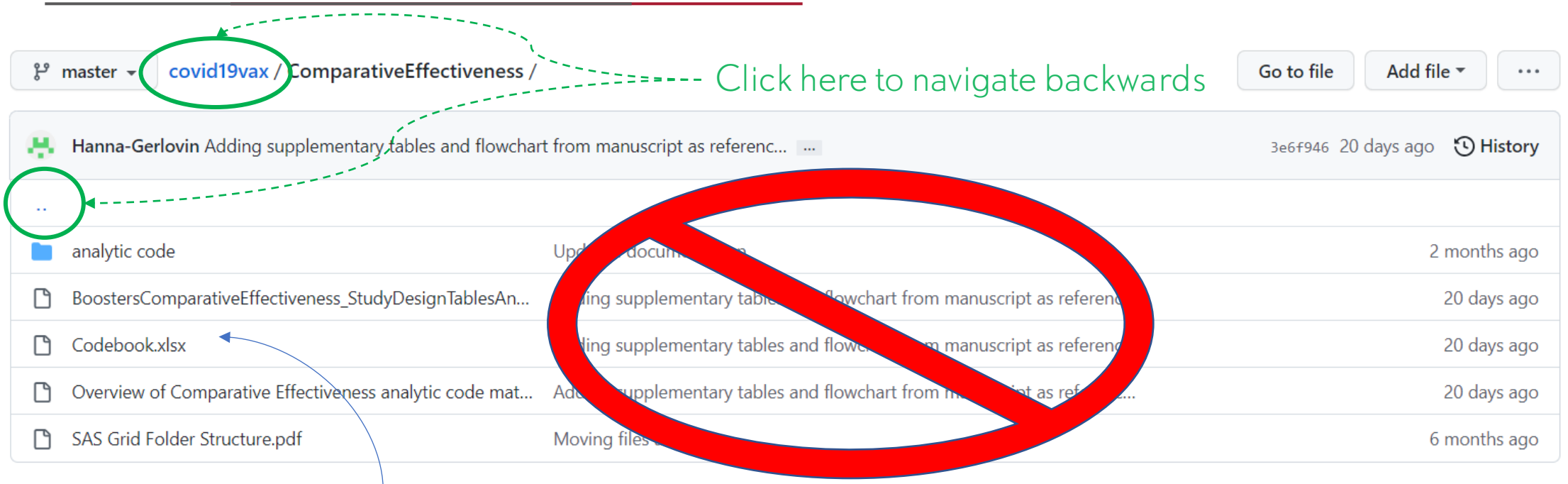
- Centralized Interactive Phenomics Resource (CIPHER)
- Partners Pages
  - VA CAUSAL
  - VA CAUSAL Methods Core
- Publications and materials

https://vhacdwdwhweb100.vha.med.va.gov/phenotype/index.php/VA_CAUSAL_Methods_Core

GitHub and General Architecture



Navigating the Materials Within GitHub EC



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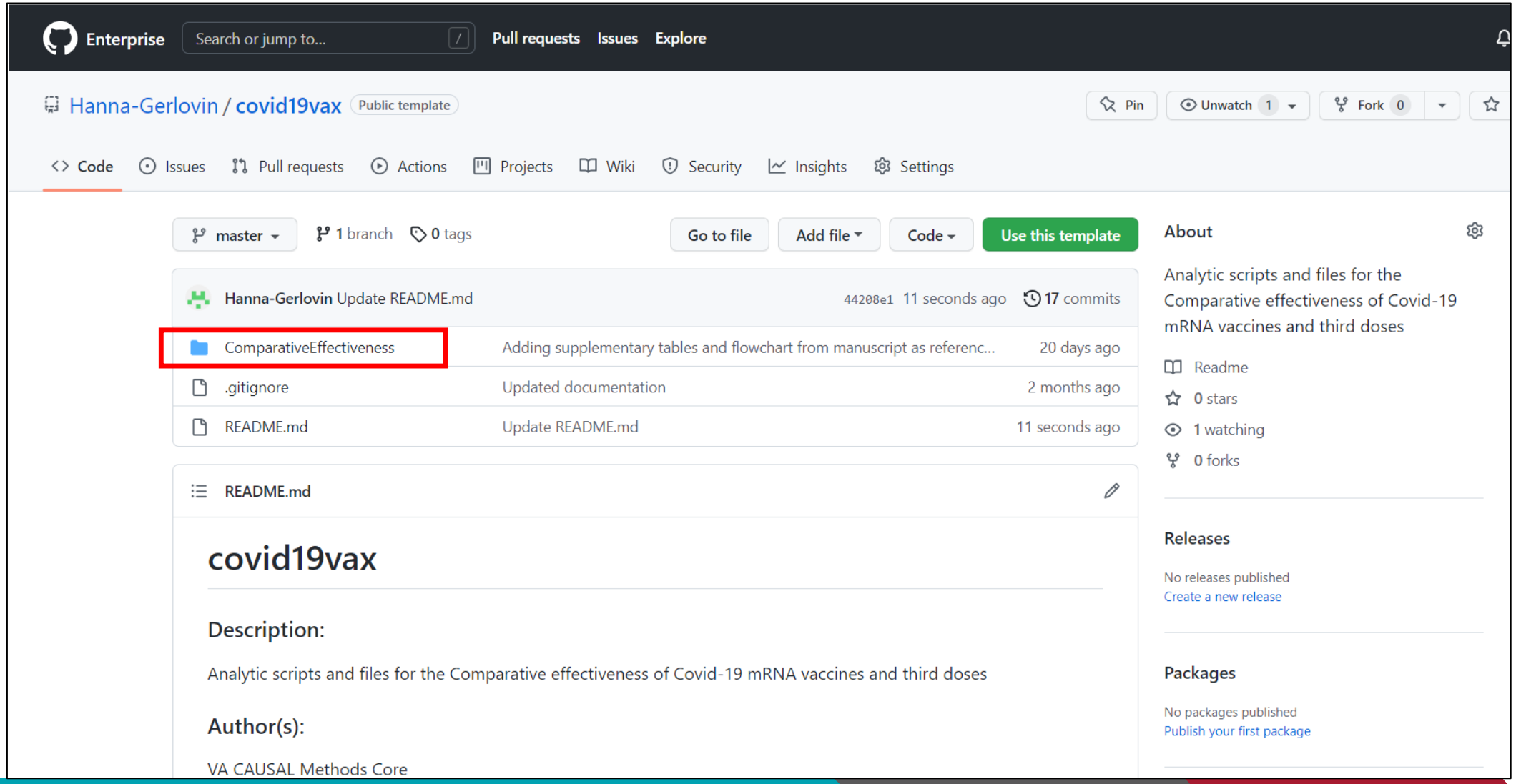
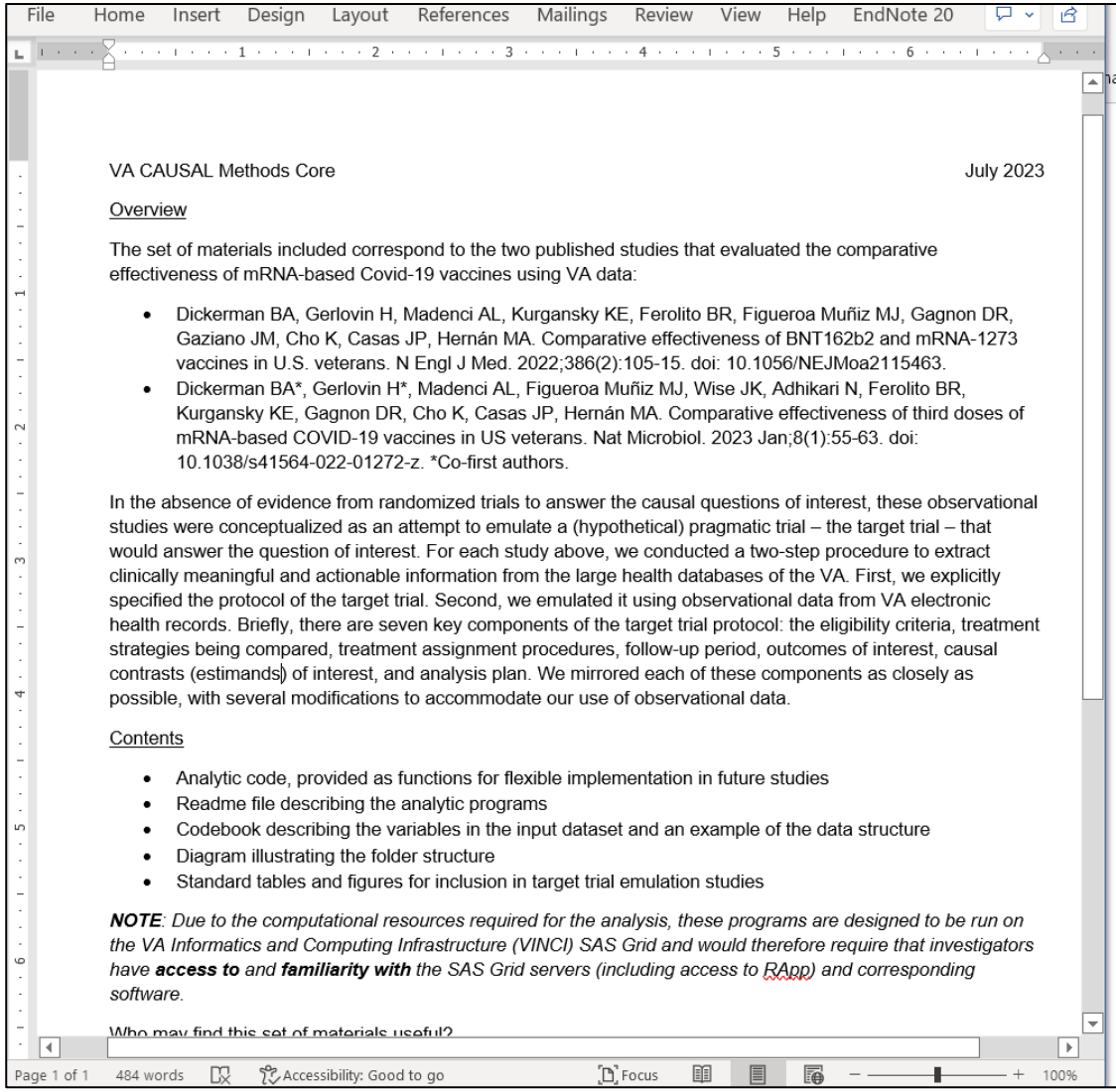
Instead, click on the individual files to see the contents inside.

Starting Point



Overview of Materials



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VA CAUSAL Methods Core July 2023

Overview

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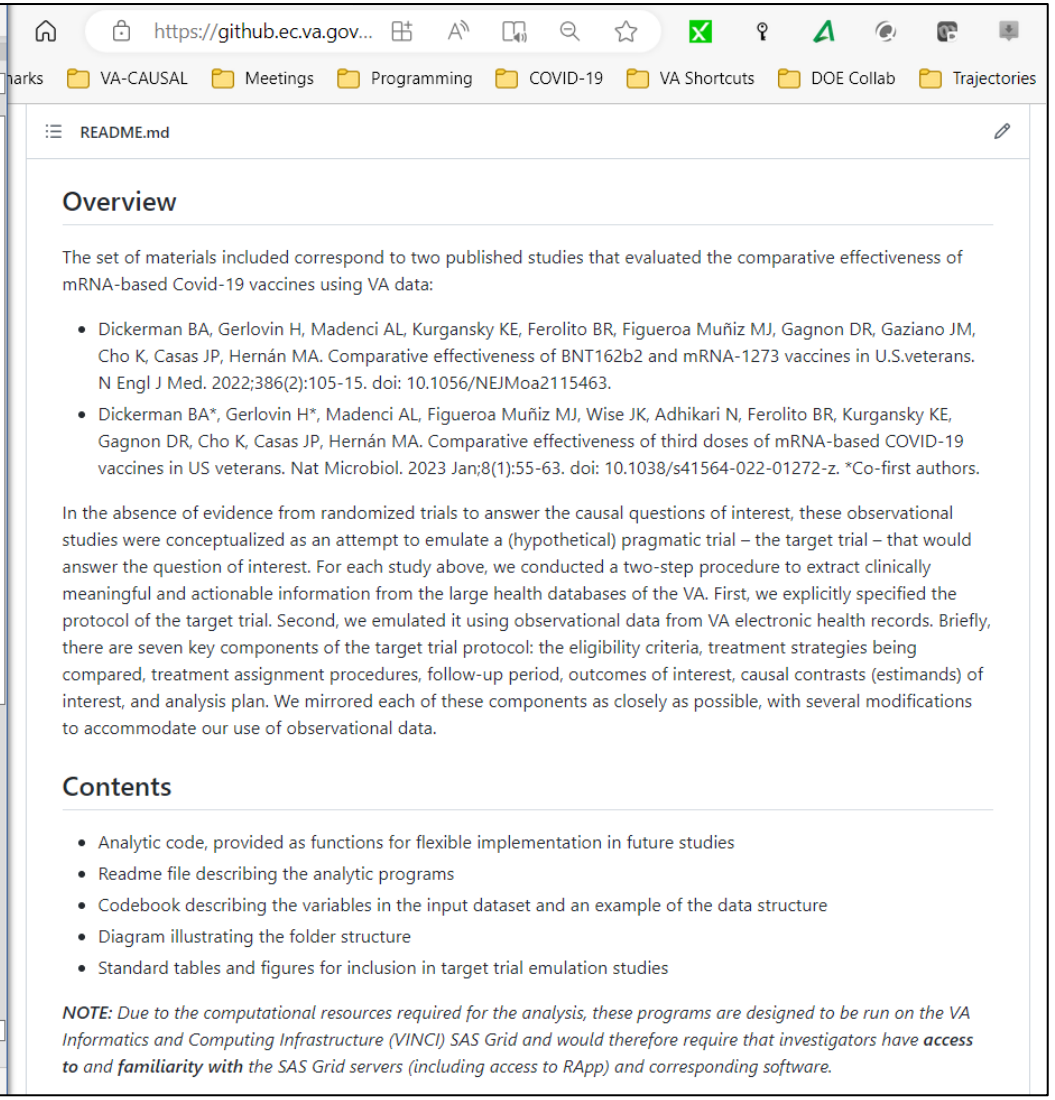
Contents

- Analytic code, provided as functions for flexible implementation in future studies
- Readme file describing the analytic programs
- Codebook describing the variables in the input dataset and an example of the data structure
- Diagram illustrating the folder structure
- Standard tables and figures for inclusion in target trial emulation studies

***NOTE**: Due to the computational resources required for the analysis, these programs are designed to be run on the VA Informatics and Computing Infrastructure (VINCI) SAS Grid and would therefore require that investigators have **access to** and **familiarity with** the SAS Grid servers (including access to RApp) and corresponding software.*

Who may find this set of materials useful?

Page 1 of 1 484 words Accessibility: Good to go Focus 100%



https://github.ec.va.gov...

VA-CAUSAL Meetings Programming COVID-19 VA Shortcuts DOE Collab Trajectories

README.md

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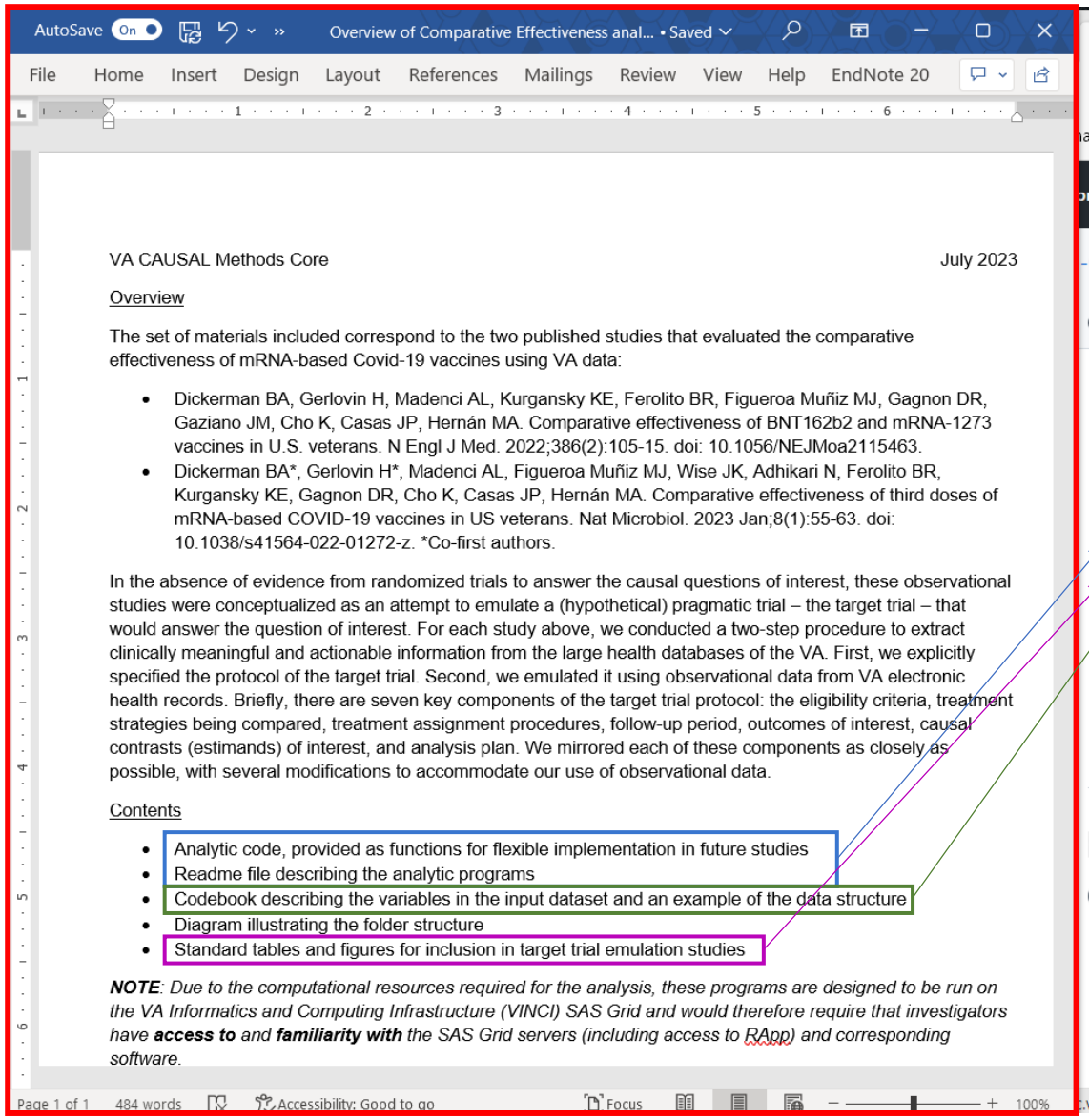

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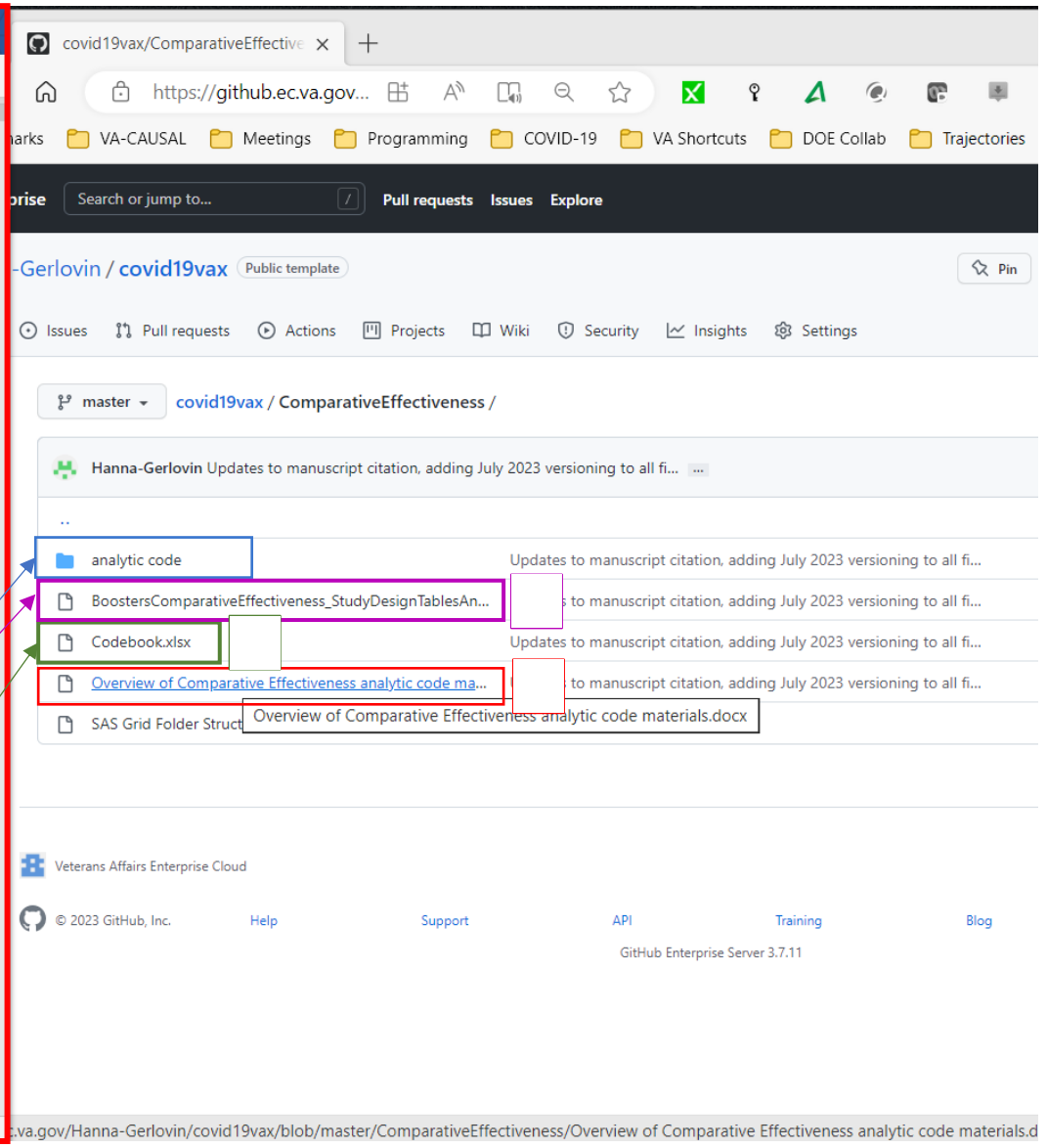
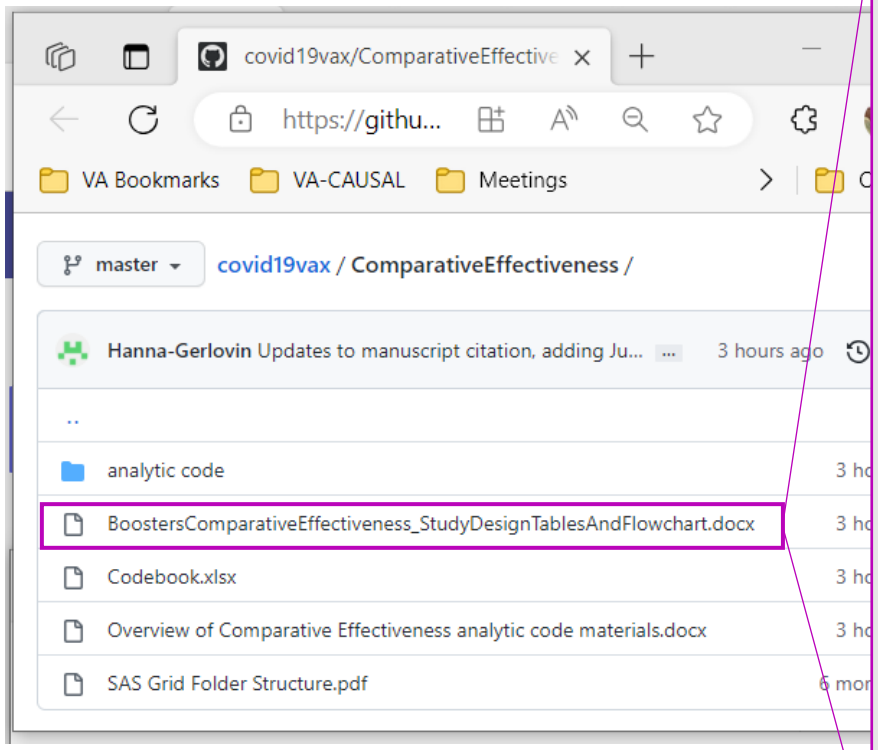
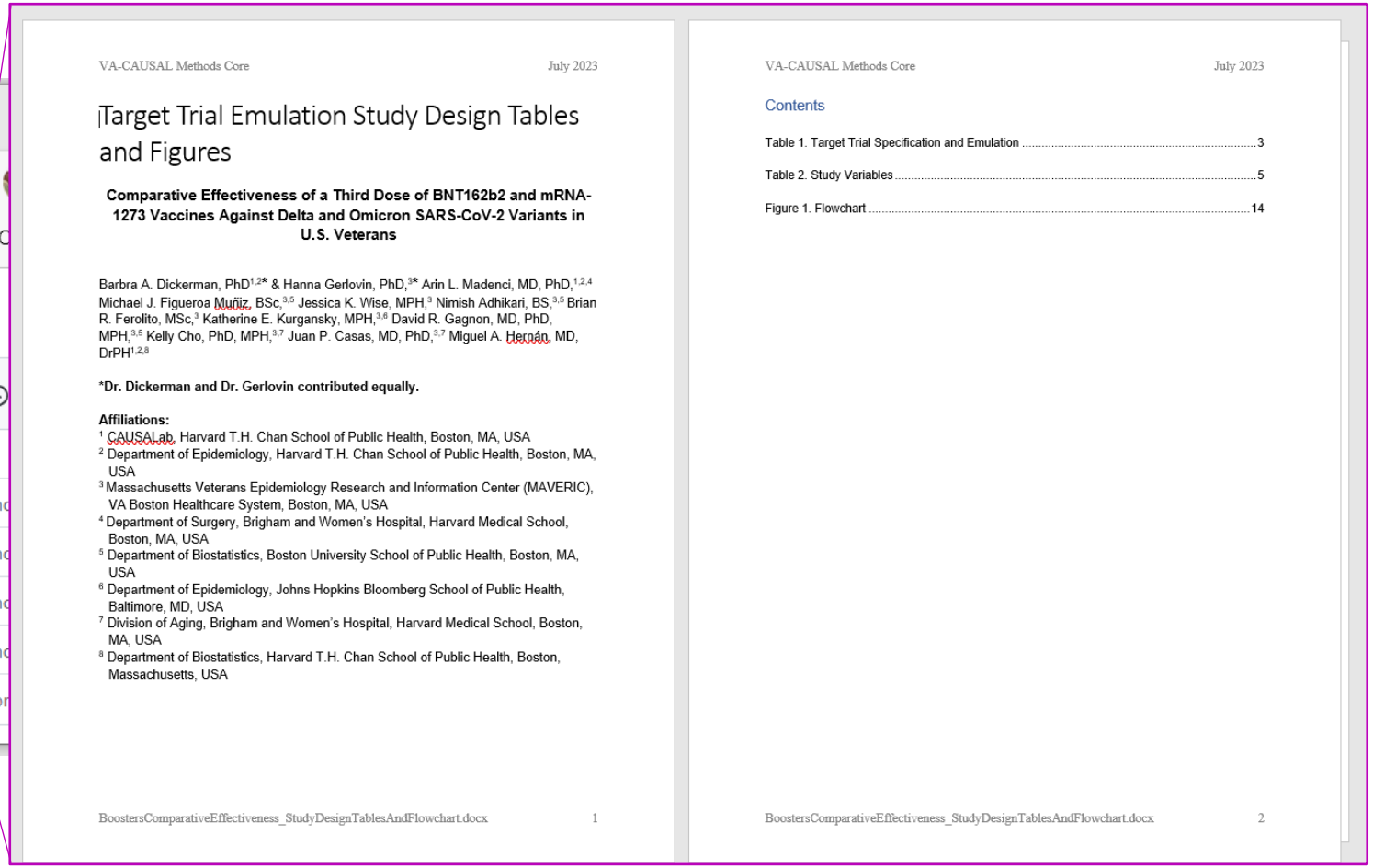


Study Design Tables and Figures





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Target Trial Emulation Study Design Tables and Figures

Comparative Effectiveness of a Third Dose of BNT162b2 and mRNA-1273 Vaccines Against Delta and Omicron SARS-CoV-2 Variants in U.S. Veterans

Barbra A. Dickerman, PhD[1,2*] & Hanna Gerlovin, PhD,[3*] Arin L. Madenci, MD, PhD,[1,2,4] Michael J. Figueroa Muñiz, BSc,[3,5] Jessica K. Wise, MPH,[3] Nimish Adhikari, BS,[3,5] Brian R. Ferolito, MSc,[3] Katherine E. Kurgansky, MPH,[3,6] David R. Gagnon, MD, PhD, MPH,[3,5] Kelly Cho, PhD, MPH,[3,7] Juan P. Casas, MD, PhD,[3,7] Miguel A. Hernán, MD, DrPH[1,2,8]

*Dr. Dickerman and Dr. Gerlovin contributed equally.

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[7] Division of Aging, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[8] Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

VA-CAUSAL Methods Core July 2023

Contents

Table 1. Target Trial Specification and Emulation

Table 1. Specification and Emulation of Target Trials Evaluating the Comparative Effectiveness of a Third Dose of the BNT162b2 and mRNA-1273 Vaccines during a Period Spanning Delta- and Omicron-Variant Predominance Using Observational Data from Veterans Health Administration Electronic Health Records (October 20, 2021–February 15, 2022).

Protocol component	Target trial specification	Target trial emulation
Eligibility criteria	• Aged ≥65 years or aged 18-64 with high risk of severe Covid-19 (based on the presence of at least one co-existing condition listed in [Manuscript] **Table 1**) between October 20, 2021, and November 18, 2021; Aged ≥18 years between November 19, 2021, and February 8, 2022 • Received the second dose of an mRNA Covid-19 vaccine primary series (same vaccine type for first and second dose) at least 6 months prior, and have not yet received a third dose • No interactions with the health care system in the past 3 days, which may indicate the start of symptomatic disease and preclude vaccination • No contraindication for Covid-19 vaccination: o Severe allergic reaction (e.g., anaphylaxis) or immediate reaction of any severity to the vaccine or any of its components o Immediate allergic reaction of any severity to polysorbate (due to potential cross-reactive hypersensitivity with the vaccine ingredient PEG) • Known residential address • Not in a long-term care facility • User of VA health care system (defined as receiving care at a station eligible to administer the vaccines under study and having at least one in-person or telehealth primary care visit in the past year) • Known smoking status and known body mass index in the past year • Have at least 7 days of potential follow-up, based on the planned end of follow-up on February 15, 2022	Same as for the target trial, except: • We identified previously documented SARS-CoV-2 infections using the VA Covid-19 National Surveillance Tool,[1] which integrates data on PCR laboratory tests with natural language processing of clinical notes to capture diagnoses inside and outside the VA system. • Data on the listed allergic reactions are not consistently available for all Veterans, but we assumed that receiving the vaccine indicates there was a determination of no previous allergic reaction.
Treatment strategies	(1) Receive a third dose of BNT162b2 vaccine at baseline, or (2) Receive a third dose of mRNA-1273 vaccine at baseline.	Same as for the target trial. We defined the date of vaccination using records in both the *Immunization* domain and procedures recorded in the *Outpatient* or *Inpatient* domains.
Treatment assignment	Individuals are randomly assigned to a strategy at baseline within strata defined by calendar date of third dose (5-day bins), calendar month of second dose (exact), age (5-year bins), sex (male, female), race (white, black, other, unknown), urbanicity of residence (urban, not urban), geographic location coded as 19 categories of Veterans Integrated Services Network, and number of SARS-CoV-2 tests performed in the past 12 months (0, 1, ≥2). Individuals will be aware of the assigned treatment strategy.	We assumed random assignment after matching eligible individuals who received a third dose of the BNT162b2 vaccine in a 1:1 ratio to eligible individuals who received a third dose of the mRNA-1273 vaccine, using the same factors used for stratified randomization as in the target trial.
Outcomes	• Documented SARS-CoV-2 infection • Symptomatic Covid-19 (defined as ≥1 of the following symptoms within 4 days of SARS-CoV-2 infection): fever, chills, cough, shortness of breath or difficulty breathing, sore throat, loss of taste or smell, headache, myalgia, diarrhea, vomiting • Hospitalization due to Covid-19 • ICU admission due to Covid-19 • Death due to Covid-19 (defined as death within 30 days of SARS-CoV-2 infection)	Same as for the target trial. We identified incident SARS-CoV-2 infections using the VA Covid-19 National Surveillance Tool, described above. We assessed symptoms using records in the *Outpatient, Inpatient, Vital Signs, Health Factors,* and *Fee* domains. We assessed VA hospitalizations using records in the *Inpatient* domain, ICU admissions using records in the *Inpatient* domain and specialty transfer codes, and deaths using records in the *Patient* domain.
Follow-up	For each person, follow-up starts on the day the third dose of vaccine was received (baseline) and ends on the day of the outcome of interest, death, 112 days (16 weeks) after baseline, or the end of the study period (February 15, 2022), whichever happens first.	Same as for the target trial.
Causal contrasts	Intention-to-treat effect. Per-protocol effect, i.e., the effect if all individuals had received the vaccination they were assigned to receive at baseline.	Observational analogue of the per-protocol effect.
Statistical analysis	Cumulative incidence (risk) curves and estimates of 16-week risk, risk differences, and risk ratios comparing the vaccination groups. Subgroup analyses by baseline age, race, time since completion of the primary series (6-7, 8, or ≥9 months), vaccine type of the primary series (BNT162b2 or mRNA-1273), previously documented SARS-CoV-2 infection.	Same as for the target trial, except we were unable to conduct subgroup analyses by previously documented SARS-CoV-2 infection (yes or no) due to lack of variability in the data.

Abbreviations: Covid-19, coronavirus disease 2019; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Table 2. Variables Used in the Analysis when Emulating a Target Trial Evaluating the Comparative Effectiveness of a Third Dose of the BNT162b2 and mRNA-1273 Vaccines Using Observational Data from Veterans Health Administration Electronic Health Records.

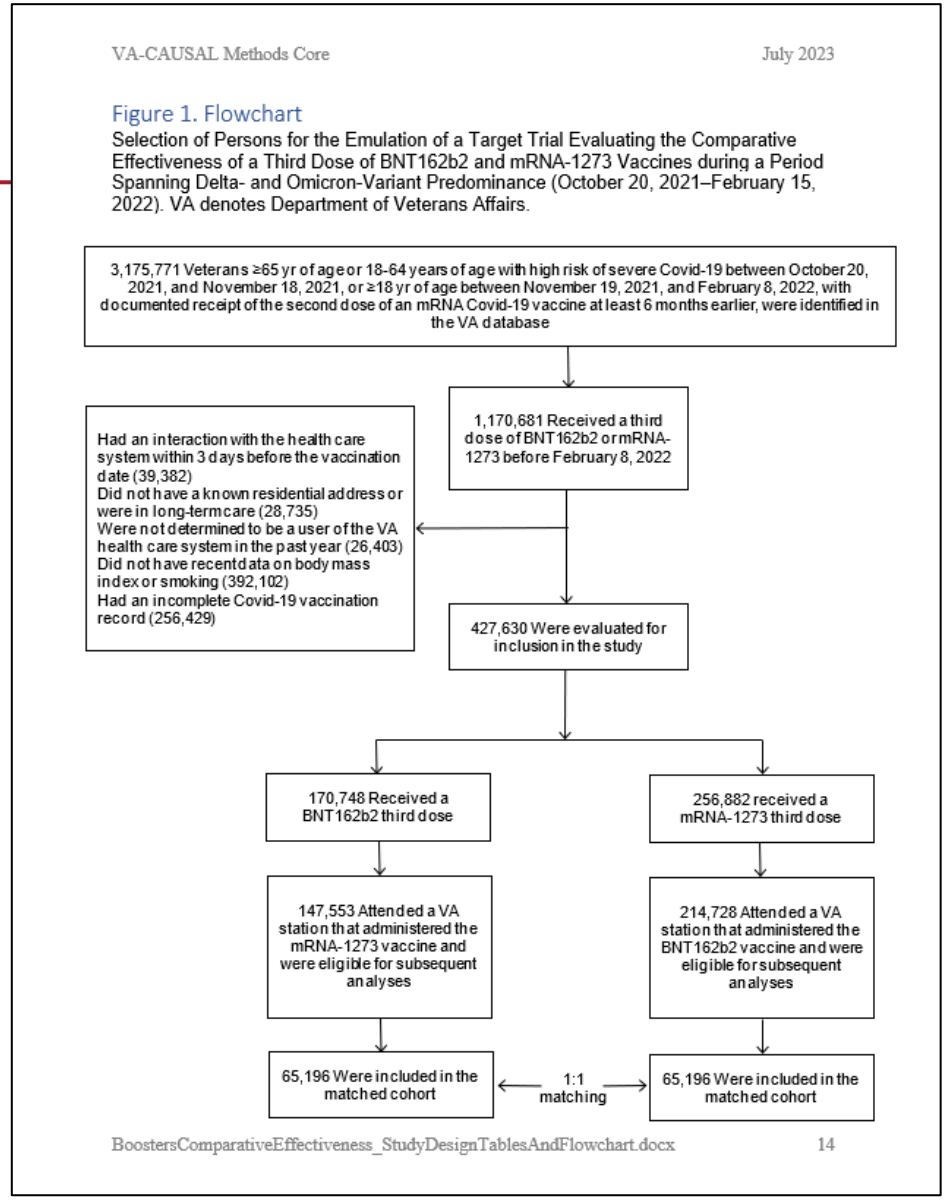
Variable	Functional form	Values	Detail	Codes
Dementia	Indicator	Yes/No	Defined as ≥2 diagnoses in the past 2 years. Based on records in the *Inpatient, Outpatient,* and *Fee* domains.	ICD10: F00%, F01%, F02%, F03%, F05.1%, G30%, G31.1%
Substance use disorder	Indicator	Yes/No	Defined as ≥2 diagnoses in the past 2 years. Based on records in the *Inpatient, Outpatient,* and *Fee* domains.	ICD10: F10.10, F10.11, F10.12%, F10.14, F10.15%, F10.18%, F10.19, F10.2%, F11.10, F11.11, F11.12%, F11.14, F11.15%, F11.18%, F11.19, F11.2%, F11.9%
Time-varying				
BNT162b2 vaccination	Indicator	Yes/No	Defined using records in both the *Immunization* domain and procedures recorded in the *Outpatient* or *Inpatient* domains. Booster doses identified by procedure codes or series designation.	CPT: 0001A, 0002A, 0003A, 0004A, 0051A, 0052A, 0053A, 0054A, 91300, 91305 CVX: 208, 217 Booster-specific CPT: 0004A, 0054A Booster Immunization Series: "B"
mRNA-1273 vaccination	Indicator	Yes/No	Defined using records in both the *Immunization* domain and procedures recorded in the *Outpatient* or *Inpatient* domains. Booster doses identified by procedure codes or series designation.	CPT: 0011A, 0012A, 0013A, 0064A, 91301, 91306 CVX: 207 Booster-specific CPT: 0064A, 91306 Boosters Immunization Series: "B"
Documented infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Indicator	Yes/No	Defined as a nasopharyngeal swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2. Identified using the VA Covid-19 National Surveillance Tool, which integrates data on laboratory tests conducted at VA clinics with natural language processing of	N/A

Table 2. Variables Used in the Analysis when Emulating a Target Trial Evaluating the Comparative Effectiveness of a Third Dose of the BNT162b2 and mRNA-1273 Vaccines Using Observational Data from Veterans Health Administration Electronic Health Records.

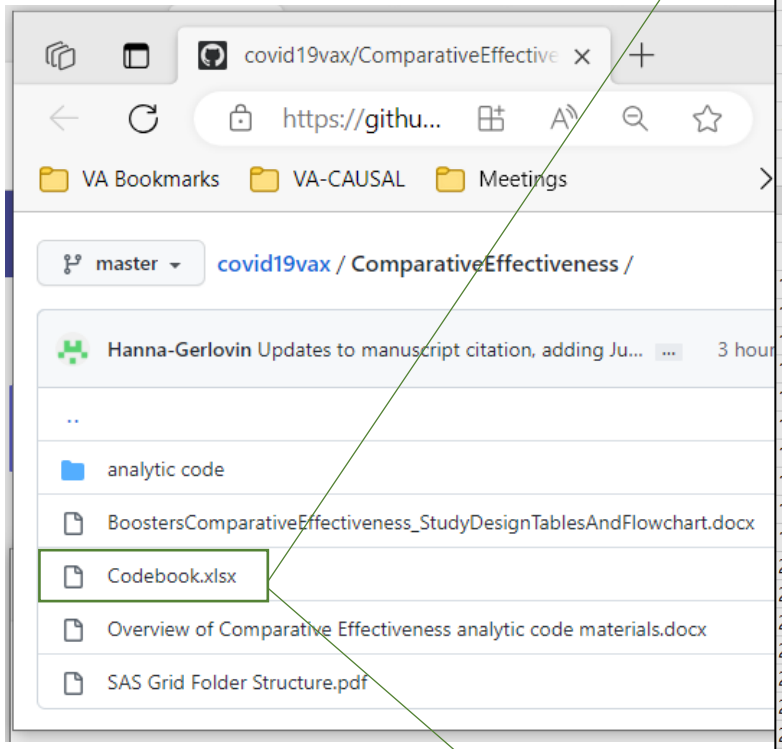
Variable	Functional form	Values	Detail	Codes
			clinical notes to capture diagnoses inside and outside the VA health care system. The algorithm to identify persons with SARS-CoV-2 infection is continually updated to ensure new annotations of Covid-19 are captured from clinical notes, with chart reviews performed periodically to validate the algorithm (11). Based on records in the Covid-19 Shared Data Resource. The event date is the specimen collection date of the first positive test during the study period.	
Symptomatic Covid-19	Indicator	Yes/No	Defined as ≥1 of the following symptoms documented within the VA health care system within 4 days after documented SARS-CoV-2 infection: fever, chills, cough, shortness of breath or difficulty breathing, sore throat, loss of taste or smell, headache, myalgia, diarrhea, vomiting. The event date is the specimen collection date. Based on records in the *Outpatient, Inpatient, Vital Signs, Health Factors,* and *Fee* domains.	Outpatient codes: ICD10: A68.9, B33.0, M79.1, M79.10, M79.11, M79.12, M79.18, R05., R06.00, R06.01, R06.02, R06.03, R06.09, R07.0, R09.3, R43.0, R43.2, R43.8, R43.9, R50.2, R50.81, R50.82, R50.83, R50.84, R50.9, R56.00, R56.01, R68.83
Hospitalization due to Covid-19	Indicator	Yes/No	Defined as a hospitalization within 21 days after documented SARS-CoV-2 infection. Based on records in the *Inpatient* domain. The event date is the hospital admission date.	N/A

Standardizing Study Design Elements

- Tables and Figures used in study design and included in the manuscript have been shared as templates for VA researchers.



Codebook



AutoSave On | Codebook.xlsx • Saved | Search (Alt+Q)

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A7 | NOTE:

	A	B	C	D
1	Codebook for variables used in the analysis of studies of the comparative effectiveness of mRNA-based Covid-19 vaccines			
2	**Accompanying the following manuscripts:**			
3	- Dickerman BA, Gerlovin H, Madenci AL, Kurgansky KE, Ferolito BR, Figueroa Muniz MJ, et al. Comparative effectiveness of BNT162b2 and mRNA-1273			
4	vaccines in U.S.veterans. N Engl J Med. 2022;386(2):105-15.			
5	- Dickerman BA*, Gerlovin H*, Madenci AL, Figueroa Muniz MJ, Wise JK, Adhikari N, et al. Comparative effectiveness of third doses of mRNA-based COVID-			
6	19 vaccines in US veterans. Nat Microbiol. 2023 Jan;8(1):55-63. *Co-first authors.			
7	**NOTE:**	The input dataset is in long-format (i.e., one row per person-time [in this case, days]). The trajectory for each individual starts on		
8		their first eligible day (baseline) and ends on the soonest of a record for the outcome of interest, death, or the administrative end		
9		of follow-up. Other applications that may consider censoring due to various mechanisms may instead end an individual's		
10		trajectory on the soonest of the outcome of interest, censoring, death, or the administrative end of follow-up.		
11	**Author(s):**	VA-CAUSAL Methods Core		
12	**Contact Information:**	This work is a product of the VA-CAUSAL Methods Core. In the near future, questions about the implementation of these		
13		programs can be directed to the VA-CAUSAL Implementation and Research Operations Core (contact information coming soon).		
14	**Version**	July 2023		
15				
16	**Codebook Tab Information**			
17	**Codebook Column**	**Description**		
18	**Variable Name**	The variable name as it should appear in the dataset being used with the programs		
19	**Definition**	Description of the variable		
20	**Code or Value**	Numeric, categorical values		
21	**Value Description**	Formats for the values		
22				
23	**ExampleLong Tab Information**			
24	This tab provides an example of the data structure for one hypothetical individual that might be included in these analyses. Each row represents a different			
25	person-day, and each column represents a different feature (baseline or time-varying). Each individual's record extends from baseline through the soonest			
26	of the outcome of interest, death, or administrative end of follow-up. This tab provides examples of records truncated upon the outcomes of Covid-19			
27	death and of any documented SARS-CoV-2 infection, to demonstrate the data inputs used in each respective analysis for this individual.			
28				
29				
30				
31				
32				
33				
34				

ReadMe | Codebook | ExampleLong

Ready | Accessibility: Investigate

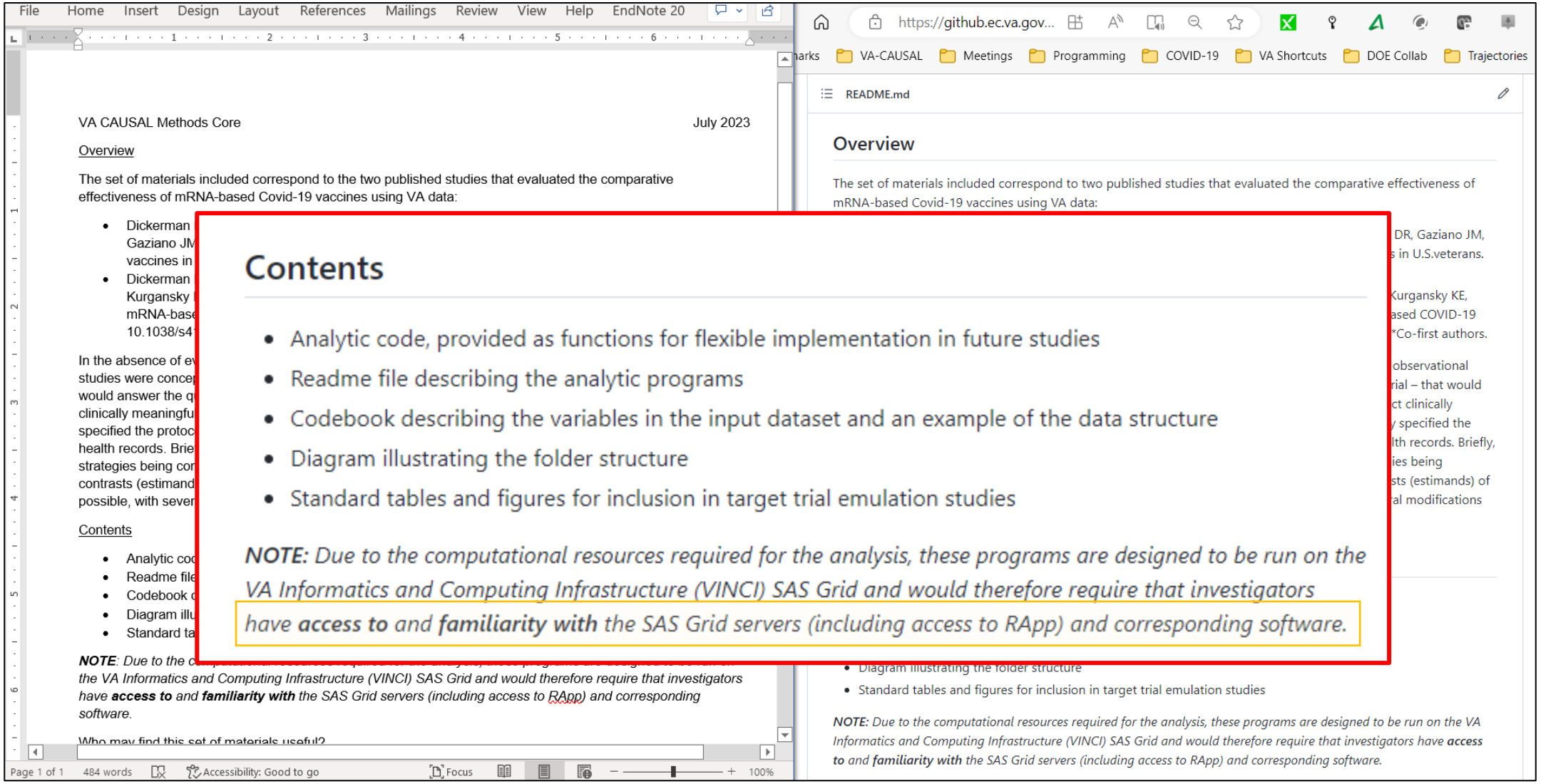
"Codebook" Tab

	A	B	C	D
1	Codebook for variables	used in the analysis of studies of the comparative effectiveness of mRNA-based Covid-19 vaccines		
2				
3	**Variable Name**	**Definition**	**Code or Value**	**Value Description**
4	Age_at_index	Age (years) at baseline	Numeric	Continuous
5	age_cat	Age (categorical) at baseline	0, 1, 2, 3, 4, 5	18-39, 40-49, 50-59, 60-69, 70-79, 80+
6	BMI	Body Mass Index (kg/m^2) at baseline	Numeric	Continuous
7	Caldate	Calendar date (daily updated)	Date	
8	COND_5yr_cancer	History of Cancer (in the past 5 years) at baseline	0, 1	No, Yes
9	COND_ckd	History of Chronic Kidney Disease (in the past 2 years) at baseline	0, 1	No, Yes
10	COND_cld	History of Chronic Liver Disease (in the past 2 years) at baseline	0, 1	No, Yes

"ExampleLong" Tab

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
1	**newid**	**caldate**	**age_at_index**	**dose3_dt**	**eligible_PM**	**keep_PM**	**PvM**	**covidpos**	**firstpos_dt**	**COVIDdeath**	**covid_dateofdeath**	**death**	**noncoviddeath**	**dateofdeath**				
2	1	1/1/2022	57	1/4/2022	0	0	1	0	1/11/2022	0	1/13/2022	0	0	1/13/2022				
3	1	1/2/2022	57	1/4/2022	0	0	1	0	1/11/2022	0	1/13/2022	0	0	1/13/2022				
4	1	1/3/2022	57	1/4/2022	0	0	1	0	1/11/2022	0	1/13/2022	0	0	1/13/2022				
5	1	1/4/2022	57	1/4/2022	1	1	1	0	1/11/2022	0	1/13/2022	0	0	1/13/2022	matching factors			
6	1	1/5/2022	57	1/4/2022	0	1	1	0	1/11/2022	0	1/13/2022	0	0	1/13/2022				
7	1	1/6/2022	57	1/4/2022	0	1	1	0	1/11/2022	0	1/13/2022	0	0	1/13/2022				
8	1	1/7/2022	57	1/4/2022	0	1	1	0	1/11/2022	0	1/13/2022	0	0	1/13/2022				
9	1	1/8/2022	57	1/4/2022	0	1	1	0	1/11/2022	0	1/13/2022	0	0	1/13/2022				
10	1	1/9/2022	57	1/4/2022	0	1	1	0	1/11/2022	0	1/13/2022	0	0	1/13/2022				
11	1	1/10/2022	57	1/4/2022	0	1	1	0	1/11/2022	0	1/13/2022	0	0	1/13/2022				
12	1	1/11/2022	57	1/4/2022	0	1	1	1	1/11/2022	0	1/13/2022	0	0	1/13/2022	observations in _covidpos dataset			
13	1	1/12/2022	57	1/4/2022	0	1	1	0	1/11/2022	0	1/13/2022	0	0	1/13/2022				
14	1	1/13/2022	57	1/4/2022	0	1	1	0	1/11/2022	1	1/13/2022	1	0	1/13/2022	observations in _COVIDdeath dataset			
15																		

Disclaimer About Analytic Programs



File Home Insert Design Layout References Mailings Review View Help EndNote 20

VA CAUSAL Methods Core July 2023

Overview

The set of materials included correspond to the two published studies that evaluated the comparative effectiveness of mRNA-based Covid-19 vaccines using VA data:

- Dickerman
  Gaziano JM
  vaccines in
- Dickerman
  Kurgansky
  mRNA-base
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Contents

- Analytic co
- Readme file
- Codebook c
- Diagram illu
- Standard ta

***NOTE**: Due to the c*
*the VA Informatics and Computing Infrastructure (VINCI) SAS Grid and would therefore require that investigators have **access to** and **familiarity with** the SAS Grid servers (including access to RApp) and corresponding software.*

Who may find this set of materials useful?

Page 1 of 1 484 words Accessibility: Good to go Focus 100%

https://github.ec.va.gov...

arks VA-CAUSAL Meetings Programming COVID-19 VA Shortcuts DOE Collab Trajectories

README.md

Overview

The set of materials included correspond to two published studies that evaluated the comparative effectiveness of mRNA-based Covid-19 vaccines using VA data:

DR, Gaziano JM,
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Kurgansky KE,
ased COVID-19
*Co-first authors.

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- Diagram illustrating the folder structure
- Standard tables and figures for inclusion in target trial emulation studies

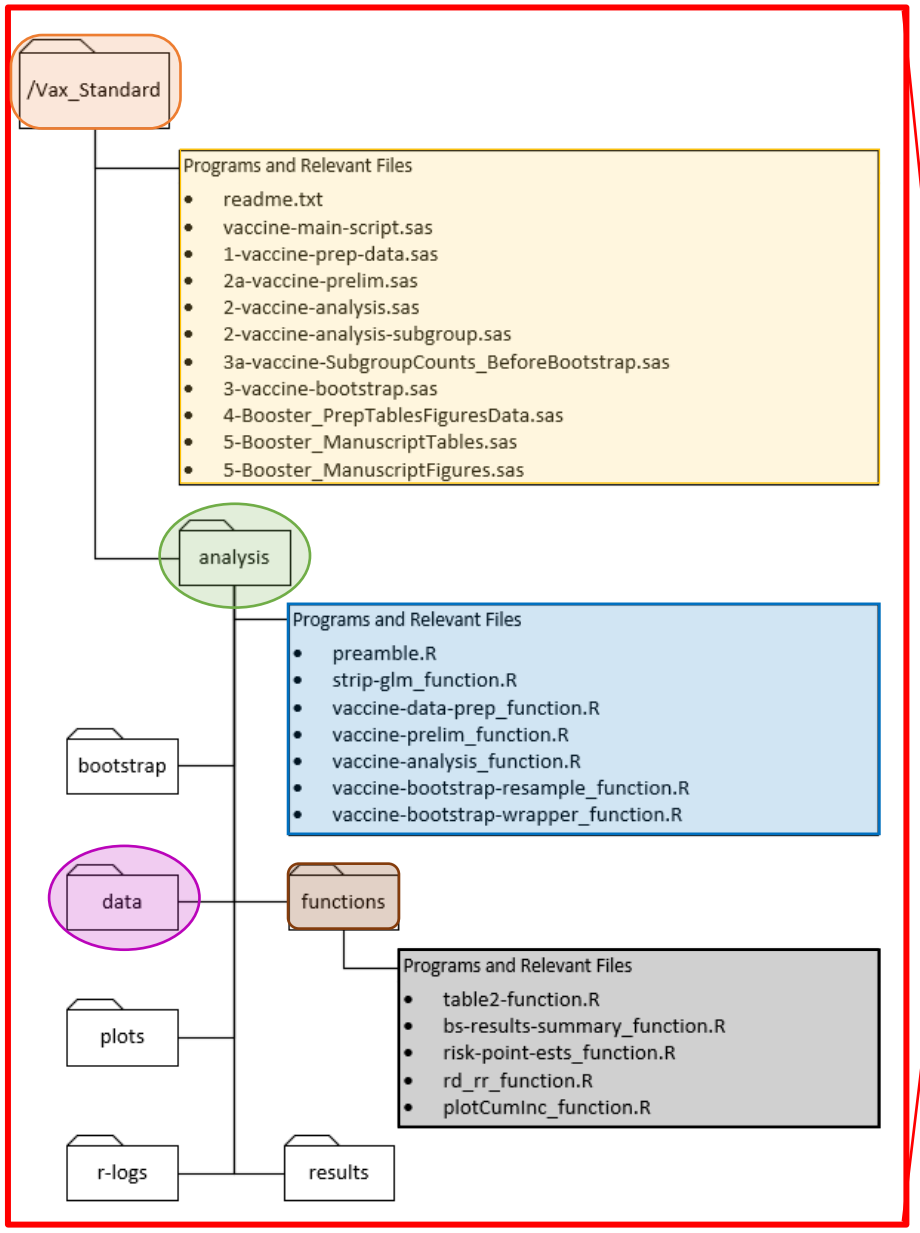
***NOTE:** Due to the computational resources required for the analysis, these programs are designed to be run on the VA Informatics and Computing Infrastructure (VINCI) SAS Grid and would therefore require that investigators have **access to** and **familiarity with** the SAS Grid servers (including access to RApp) and corresponding software.*

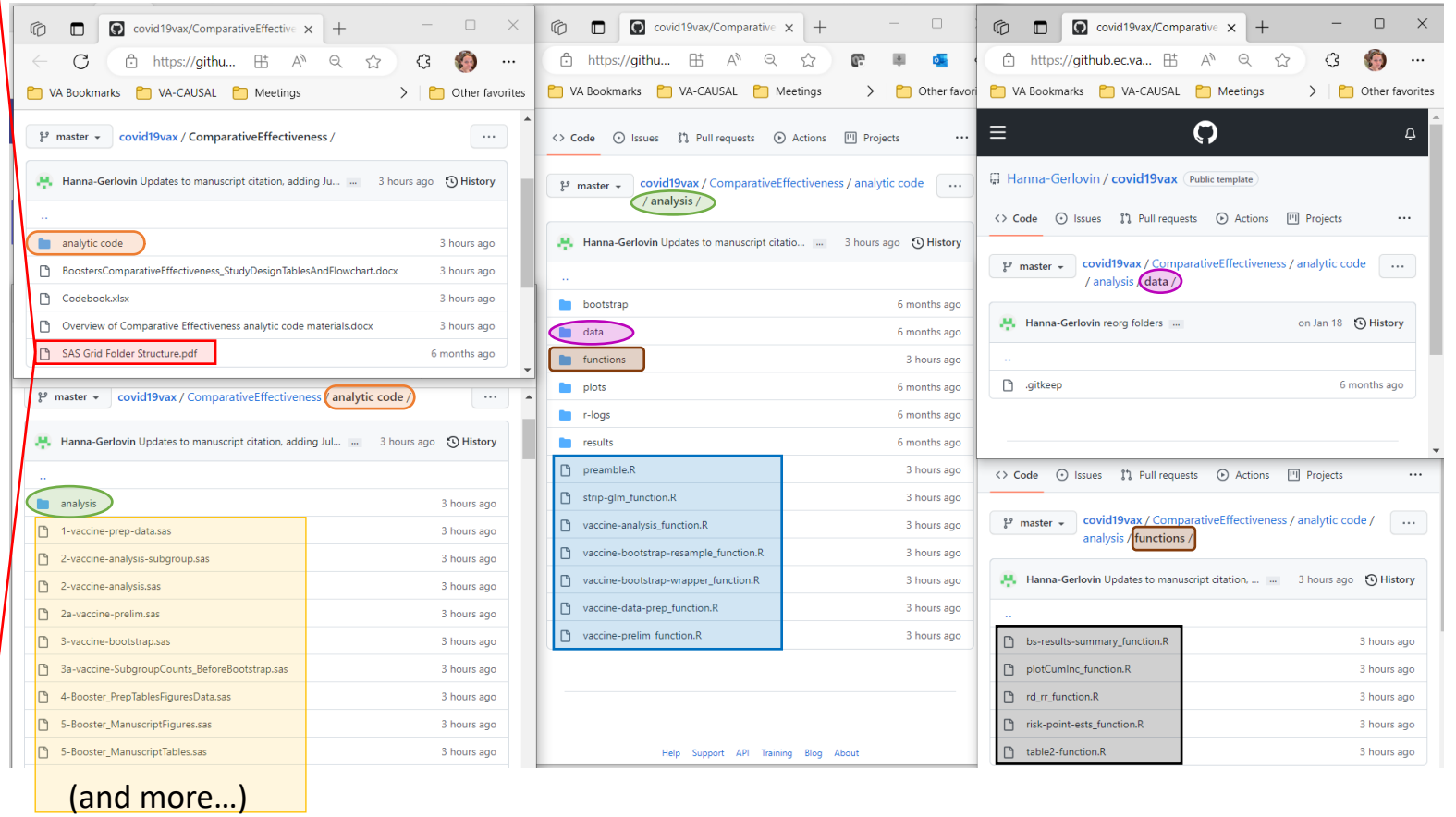
Contents

- Analytic code, provided as functions for flexible implementation in future studies
- Readme file describing the analytic programs
- Codebook describing the variables in the input dataset and an example of the data structure
- Diagram illustrating the folder structure
- Standard tables and figures for inclusion in target trial emulation studies

***NOTE:** Due to the computational resources required for the analysis, these programs are designed to be run on the VA Informatics and Computing Infrastructure (VINCI) SAS Grid and would therefore require that investigators have **access to** and **familiarity with** the SAS Grid servers (including access to RApp) and corresponding software.*

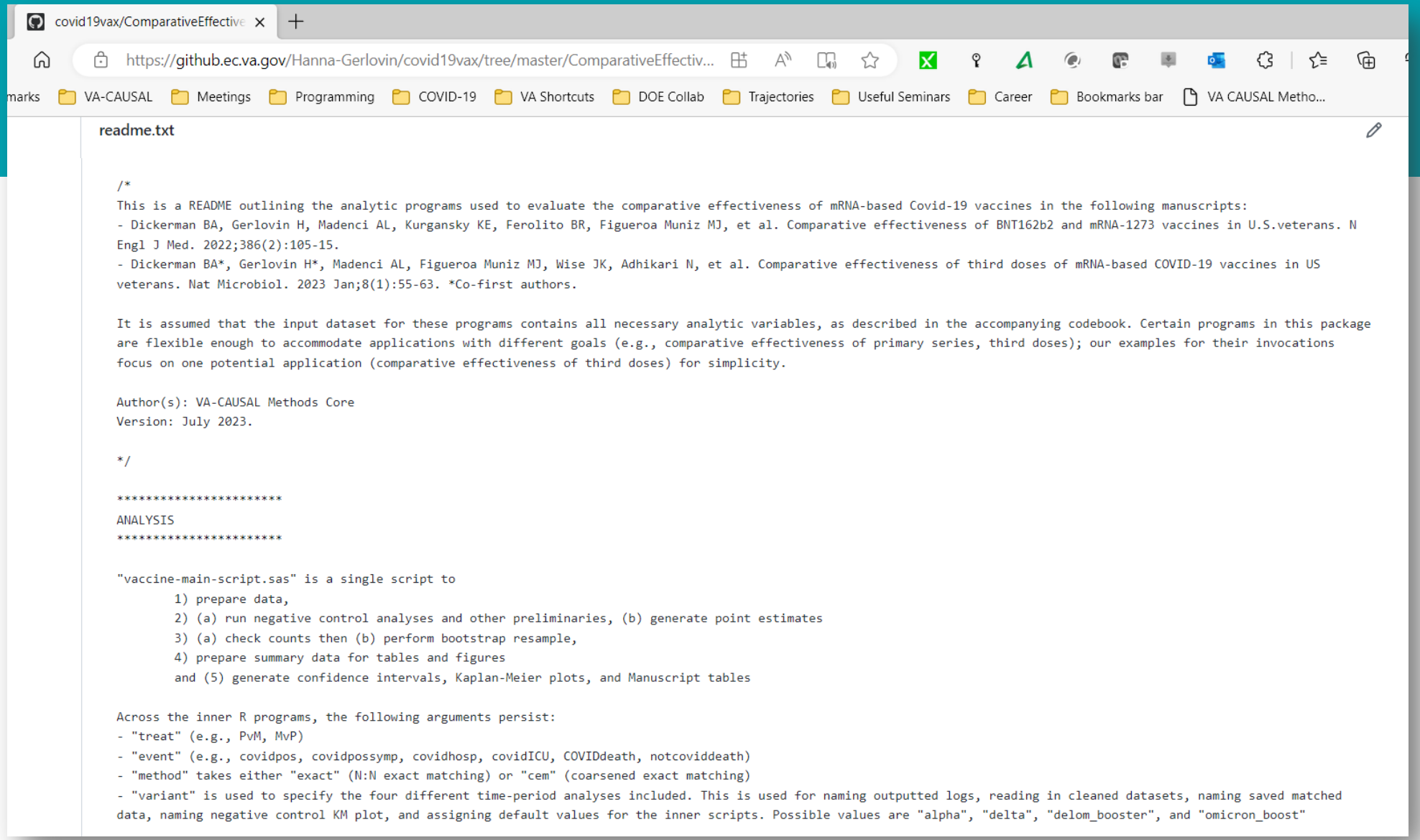
Diagram Illustrating the Folder Structure



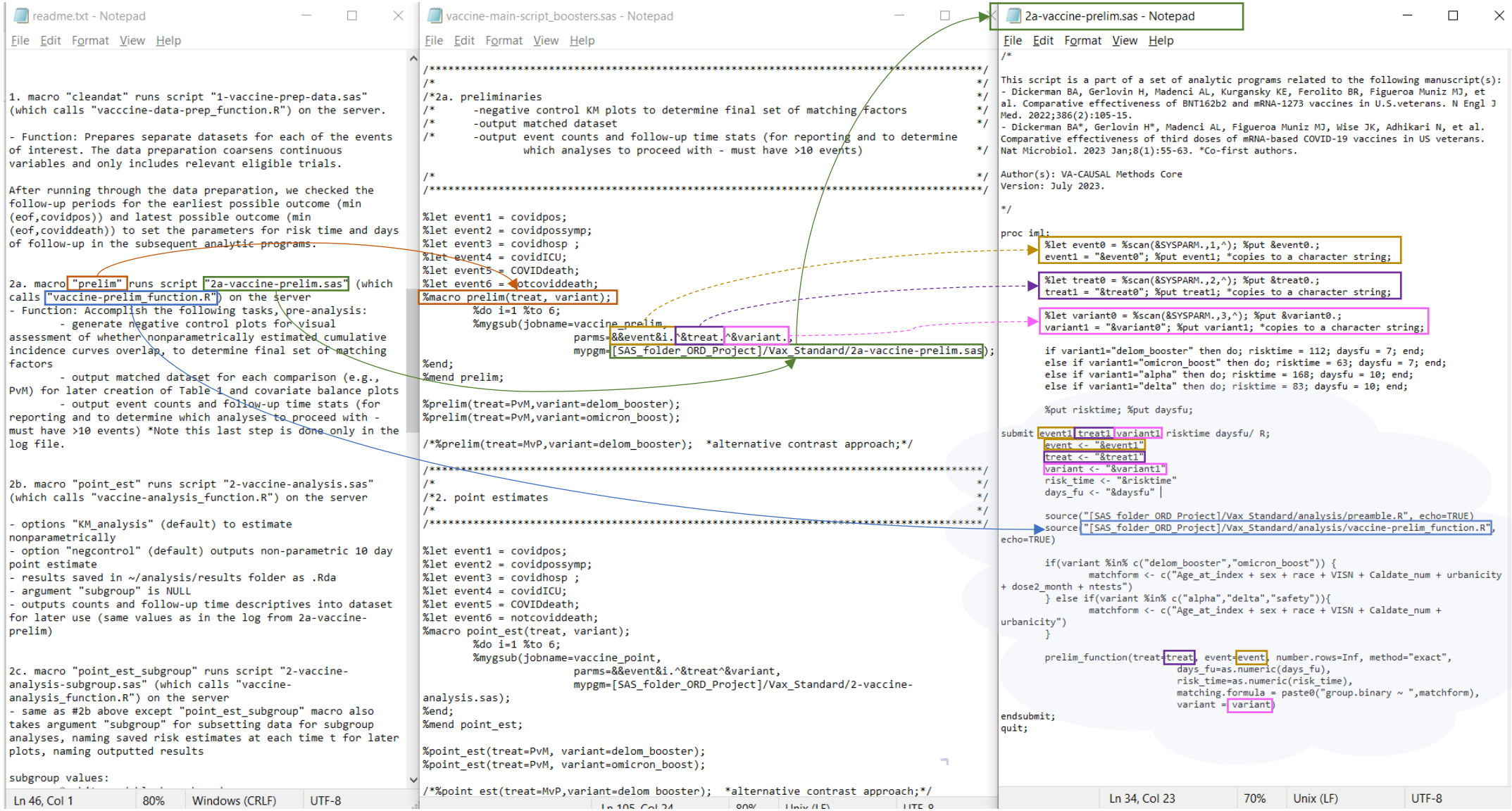


(and more…)

Navigating the readme and scripts



Example: %prelim() and 2a-vaccine-prelim.sas



readme.txt - Notepad

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```
1. macro "cleandat" runs script "1-vaccine-prep-data.sas"
(which calls "vacccine-data-prep_function.R") on the server.

- Function: Prepares separate datasets for each of the events
of interest. The data preparation coarsens continuous
variables and only includes relevant eligible trials.

After running through the data preparation, we checked the
follow-up periods for the earliest possible outcome (min
(eof,covidpos)) and latest possible outcome (min
(eof,coviddeath)) to set the parameters for risk time and days
of follow-up in the subsequent analytic programs.


2a. macro "prelim" runs script "2a-vaccine-prelim.sas" (which
calls "vaccine-prelim_function.R") on the server
- Function: Accomplish the following tasks, pre-analysis:
        - generate negative control plots for visual
assessment of whether nonparametrically estimated cumulative
incidence curves overlap, to determine final set of matching
factors
        - output matched dataset for each comparison (e.g.,
PvM) for later creation of Table 1 and covariate balance plots
        - output event counts and follow-up time stats (for
reporting and to determine which analyses to proceed with -
must have >10 events) *Note this last step is done only in the
log file.


2b. macro "point_est" runs script "2-vaccine-analysis.sas"
(which calls "vaccine-analysis_function.R") on the server

- options "KM_analysis" (default) to estimate
nonparametrically
- option "negcontrol" (default) outputs non-parametric 10 day
point estimate
- results saved in ~/analysis/results folder as .Rda
- argument "subgroup" is NULL
- outputs counts and follow-up time descriptives into dataset
for later use (same values as in the log from 2a-vaccine-
prelim)


2c. macro "point_est_subgroup" runs script "2-vaccine-
analysis-subgroup.sas" (which calls "vaccine-
analysis_function.R") on the server
- same as #2b above except "point_est_subgroup" macro also
takes argument "subgroup" for subsetting data for subgroup
analyses, naming saved risk estimates at each time t for later
plots, naming outputted results

subgroup values:
```

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vaccine-main-script_boosters.sas - Notepad

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```
/*****************************************************************************/
/*                                                                           */
/*2a. preliminaries                                                          */
/*      -negative control KM plots to determine final set of matching factors*/
/*      -output matched dataset                                              */
/*      -output event counts and follow-up time stats (for reporting and to determine
            which analyses to proceed with - must have >10 events)           */
/*                                                                           */
/*****************************************************************************/

%let event1 = covidpos;
%let event2 = covidpossymp;
%let event3 = covidhosp ;
%let event4 = covidICU;
%let event5 = COVIDdeath;
%let event6 = notcoviddeath;
%macro prelim(treat, variant);
        %do i=1 %to 6;
        %mygsub(jobname=vaccine_prelim,
                        parms=&&event&i.^&treat.^&variant.,
                        mypgm=[SAS_folder_ORD_Project]/Vax_Standard/2a-vaccine-prelim.sas);
%end;
%mend prelim;

%prelim(treat=PvM,variant=delom_booster);
%prelim(treat=PvM,variant=omicron_boost);

/*%prelim(treat=MvP,variant=delom_booster);  *alternative contrast approach;*/

/*****************************************************************************/
/*                                                                           */
/*2. point estimates                                                         */
/*                                                                           */
/*****************************************************************************/

%let event1 = covidpos;
%let event2 = covidpossymp;
%let event3 = covidhosp ;
%let event4 = covidICU;
%let event5 = COVIDdeath;
%let event6 = notcoviddeath;
%macro point_est(treat, variant);
        %do i=1 %to 6;
        %mygsub(jobname=vaccine_point,
                        parms=&&event&i.^&treat^&variant,
                        mypgm=[SAS_folder_ORD_Project]/Vax_Standard/2-vaccine-
analysis.sas);
%end;
%mend point_est;

%point_est(treat=PvM, variant=delom_booster);
%point_est(treat=PvM, variant=omicron_boost);

/*%point_est(treat=MvP,variant=delom_booster);  *alternative contrast approach;*/
```

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2a-vaccine-prelim.sas - Notepad

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```
/*

This script is a part of a set of analytic programs related to the following manuscript(s):
- Dickerman BA, Gerlovin H, Madenci AL, Kurgansky KE, Ferolito BR, Figueroa Muniz MJ, et
al. Comparative effectiveness of BNT162b2 and mRNA-1273 vaccines in U.S.veterans. N Engl J
Med. 2022;386(2):105-15.
- Dickerman BA*, Gerlovin H*, Madenci AL, Figueroa Muniz MJ, Wise JK, Adhikari N, et al.
Comparative effectiveness of third doses of mRNA-based COVID-19 vaccines in US veterans.
Nat Microbiol. 2023 Jan;8(1):55-63. *Co-first authors.

Author(s): VA-CAUSAL Methods Core
Version: July 2023.

*/

proc iml;
        %let event0 = %scan(&SYSPARM.,1,^); %put &event0.;
        event1 = "&event0"; %put event1; *copies to a character string;

        %let treat0 = %scan(&SYSPARM.,2,^); %put &treat0.;
        treat1 = "&treat0"; %put treat1; *copies to a character string;

        %let variant0 = %scan(&SYSPARM.,3,^); %put &variant0.;
        variant1 = "&variant0"; %put variant1; *copies to a character string;

        if variant1="delom_booster" then do; risktime = 112; daysfu = 7; end;
        else if variant1="omicron_boost" then do; risktime = 63; daysfu = 7; end;
        else if variant1="alpha" then do; risktime = 168; daysfu = 10; end;
        else if variant1="delta" then do; risktime = 83; daysfu = 10; end;

        %put risktime; %put daysfu;

submit event1 treat1 variant1 risktime daysfu/ R;
        event <- "&event1"
        treat <- "&treat1"
        variant <- "&variant1"
        risk_time <- "&risktime"
        days_fu <- "&daysfu"

        source("[SAS_folder_ORD_Project]/Vax_Standard/analysis/preamble.R", echo=TRUE)
        source("[SAS_folder_ORD_Project]/Vax_Standard/analysis/vaccine-prelim_function.R",
echo=TRUE)

        if(variant %in% c("delom_booster","omicron_boost")) {
                matchform <- c("Age_at_index + sex + race + VISN + Caldate_num + urbanicity
+ dose2_month + ntests")
        } else if(variant %in% c("alpha","delta","safety")){
                matchform <- c("Age_at_index + sex + race + VISN + Caldate_num +
urbanicity")
        }

        prelim_function(treat=treat, event=event, number.rows=Inf, method="exact",
                        days_fu=as.numeric(days_fu),
                        risk_time=as.numeric(risk_time),
                        matching.formula = paste0("group.binary ~ ",matchform),
                        variant = variant)
endsubmit;
quit;
```

Ln 34, Col 23 | 70% | Unix (LF) | UTF-8

R code within SAS Grid*

* https://vincicentral.vinci.med.va.gov/SitePages/VINCI_University-SAS_Grid.aspx – Go to "Select SAS/Grid Guides" for more information

Example: prelim_function()

covid19vax / ComparativeEffectiveness / analytic code / analysis / **vaccine-prelim_function.R**

Hanna-Gerlovin Updates to manuscript citation, adding July 2023 versioning t... ... History

1 contributor

157 lines (137 sloc) | 9.45 KB

```
1   #####
2   #
3   # This script is a part of a set of analytic programs related to the following manuscript(s):
4   #  - Dickerman BA, Gerlovin H, Madenci AL, Kurgansky KE, Ferolito BR, Figueroa Muniz MJ, et al. (
5   #  - Dickerman BA*, Gerlovin H*, Madenci AL, Figueroa Muniz MJ, Wise JK, Adhikari N, et al. Compa
6   #
7   # Author(s): VA-CAUSAL Methods Core
8   # Version: July 2023.
9   #
10  ######
11
12  prelim_function <- function(event="covidpos", treat="PvM", days_fu=7, risk_time=168,
13                              method=c("exact", "cem"),
14                              matching.formula = paste0("group.binary ~ Age_at_index + sex + race
15                              number.rows=Inf, variant="alpha"
16
17
18    # Load the server/path specifications for the R session
19    preamble(...); source(paste0(prefix, "/strip-glm_function.R"))
20
21    # Initialize an r-log
22    if(server){
23      my_log <<- file(paste0(prefix, "/r-logs/log-vaccine-prelim-", treat, "-", event,"-",method,"-
24      sink(my_log, append=TRUE)
25      sink(my_log, append=TRUE, type="message")
26    }
27
28    print(variant)
29
30     #define legend labels based on supplied treat variable
31     legend_treat1 <- fcase(treat=="PvM","BNT162b2",
32                    treat=="MvP","mRNA-1273")
33
```

1 – setup the function and defaults

2 – load program dependencies

3 – initialize the logs

4 – perform matching with pre-specified seed

```
37    # Perform matching to allow for preliminary checks
38      if(method=="exact"){
39         set.seed(5)
40       m.out <- match.data(matchit(formula = as.formula(matching.formula),
41                                   data=fread(file=paste0(prefix, "/data/cleaned-
42                                     filter(!is.na(Age_at_index)), # removed n=2
43                                   method="exact",
44                                   verbose=TRUE, #progress bar
45                                   k2k=TRUE))[,.(newid, group.binary, outcome, ne
46       n_1 <- unique(m.out[group.binary==1,][,num_1 := .N, by=.(subclass)][, .(su
47       n_0 <- unique(m.out[group.binary==0][, num_0 := .N, by=.(subclass)][, .(su
48       n <- n_1[n_0, on=.(subclass)][, num := pmin(num_1, num_0)][]
49       m.out.num <- n[m.out, on = .(subclass)][]
50       m.out <- rbindlist(list(m.out.num[group.binary==0,][, .SD[sample(x=.N, siz
51                               m.out.num[group.binary==1,][, .SD[sample(x=.N, siz
52     }
53     if(method=="cem"){
54        set.seed(5)
55
56                if(variant %in% c("alpha","delta")) {
57                m.out <- match.data(matchit(formula = as.formula(matching.formul
58                                    data=fread(file=paste0(prefix, "/data/cleaned-
87        }
88
89    print("matching done")
90
91
92          # May want to uncomment the bracketed lines to not save the datasets for
93     #if(event=="covidpos"){
94                fwrite(m.out[,.(newid, group.binary, outcome, newperiod, subclas
95                file=paste0(prefix, "/data/matched-dat-",treat,"-",event,"-",met
96     #}
97
98     # Save descriptives to log for preliminary checks
99    print(paste("Matched data, number of treat1 for",treat,"comparison:",table(m.c
100   print(paste("Matched data, number of treat0 for",treat,"comparison:",table(m.c
101   print(paste("Matched data, number of events, total:",table(m.out$outcome[m.out
102   print(paste("Matched data, number of events, in treat1:",table(m.out$outcome[m
103   print(paste("Matched data, number of events, in treat0:",table(m.out$outcome[m
104   print(paste("Matched data, follow-up time, median:",quantile(pmin(m.out$days,r
105   print(paste("Matched data, follow-up time, 25th percentile:",quantile(pmin(m.c
106   print(paste("Matched data, follow-up time, 75th percentile:",quantile(pmin(m.c
107   print(paste("Matched data (treat=1), follow-up time, median:",quantile(pmin(m.
108
```

5 – save the matched data for use in tables

6 – print event counts and preliminary statistics to log

7 – fit a Kaplan-Meier survival model for first X days

```
115     # Check the Kaplan-Meier curves for first 7-10 days (negative control, no ex
116     km.data <- survfit(Surv(days, outcome) ~ group.binary, data=m.out %>%
117                        mutate(group.binary = factor(group.binary)) %>%
118                        mutate(group.binary = forcats::fct_relevel(group.binary
119
120     mypal=ggsci::pal_jama("default",alpha=1)(2)
121
122     neg.control.km.plot <- suppressWarnings(survminer::ggsurvplot(km.data, data=
123                                                                   palette = c(mypal[1
124                                                                   size=1,
125                                                                   censor=FALSE,
126                                                                   fun="event",
127                                                                   linetype=c(1,2),
128                                                                   font.main=24,
129                                                                   legend=c(0.12, 0.8)
130                                                                   legend.title="",
131                                                                   legend.labs=c(paste
132                                                                   risk.table=TRUE,
133                                                                   risk.table.height =
134                                                                   tables.y.text.col=F
135                                                                   fontsize=10,
136                                                                   xlim=c(0,days_fu),
137                                                                   break.x.by=1,
138                                                                   xlab="Days",
139                                                                   ylim=c(0,0.005),
140                                                                   surv.scale="percent
141                                                                   ylab="Cumulative in
142                                                                   ggtheme=theme_survm
143
144
145
148
149                                                                   tables.theme=theme_
150
151
152     #save negative control KM plot (pdf)
153     pdf(paste0(prefix,"/plots/figure-neg-control-km-plot_",treat,"-",event,"-",m
154     print(neg.control.km.plot,newpage=FALSE)
155     dev.off()
156
157   }
```

8 – build the negative control plot

9 – save the PDF plot

Who may find this set of materials useful?

- Point interventions (administered at a single point in time)
- Baseline confounders only (here, adjustment is made via matching)
- Non-parametric estimator (Kaplan-Meier)
- Non-parametric bootstrap procedure (including both matching and subsequent analyses) to calculate percentile-based 95% confidence intervals for all estimates

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- Covid-19 Shared Data Resource
- Centralized Interactive Phenomics Resource (CIPHER)
- MVP Data Core

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