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

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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

Received: 28 July 2022	Barbra A. Dickerman 🕲 ^{1.2,9} , Hanna Gerlovin 🕲 ^{3,9} 🖂, Arin L. Madenci 🕲 ^{1.2,4} ,
Accepted: 17 October 2022	Michael J. Figueroa Muñiz ^{3,5} , Jessica K. Wise ³ , Nimish Adhikari ^{3,5} , Brian R. Ferolito ³ , Katherine E. Kurgansky ^{3,6} , David R. Gagnon ^{3,5} , Kelly Cho ^{3,7} ,
Published online: 02 January 2023	Juan P. Casas ^{3,7} & Miguel A. Hernán ^(D) ^{1,2,8}

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
 - o 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
 - o In time periods spanning SARS-CoV-2 delta- and omicron-variant predominance, and restricted to omicron-variant predominance



Protocol of a ta	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	 Third dose of BNT162b2 vaccine at baseline 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

o Target trial described

Period restricted to omicron-variant predominance

- o A second identical target trial, except
 - o Recruitment: January 1 to March 1, 2022
 - o 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

o Largest integrated healthcare system in the U.S.

VA Corporate Data Warehouse (CDW)

o Detailed information on demographics, inpatient and outpatient encounters, medications, laboratory results

o Data refreshed nightly

o Decades of follow-up



Mapping variables to the available data



Variable

Covid-19 vaccination

SARS-CoV-2 infection

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)

Covid-19 related hospitalization

(a hospitalization within 21 days of infection)

Covid-19 related ICU admission

(an ICU admission during a Covid-19 hospitalization)

Covid-19 death

(a death within 30 days of SARS-CoV-2 infection)

Ascertainment

Records in *Immunization* domain and procedures recorded in *Outpatient* or *Inpatient* domains

VA Covid-19 National Surveillance Tool

Records in *Outpatient*, *Inpatient*, *Vital Signs*, *Health Factors*, and *Fee* domains

Records in Inpatient domain

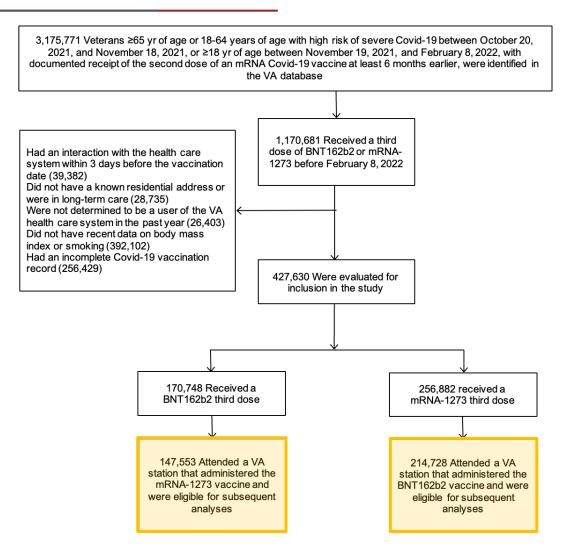
Records in *Inpatient* domain and specialty transfer codes

Records in *Patient* domain





Applied the same eligibility criteria to Veterans in the database





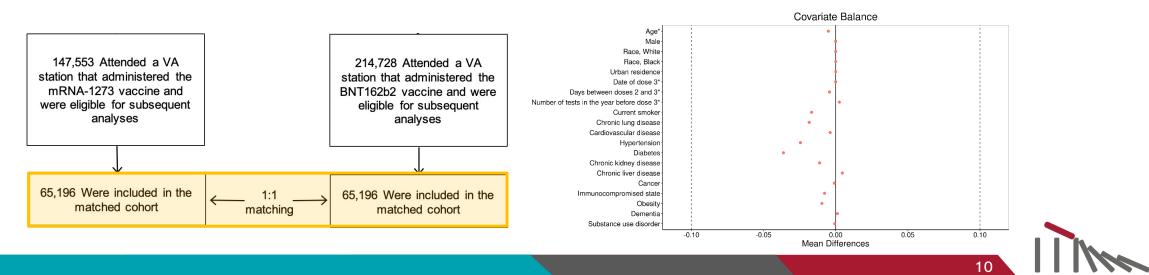
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Closely matched recipients of each vaccine



 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

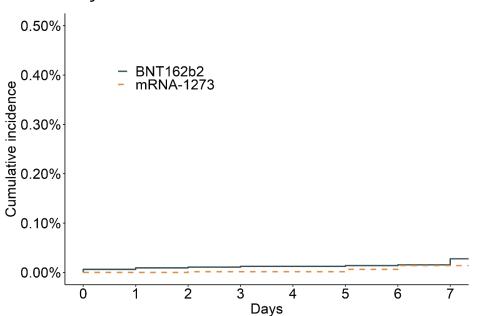
All measured variables were well-balanced between the 2 groups



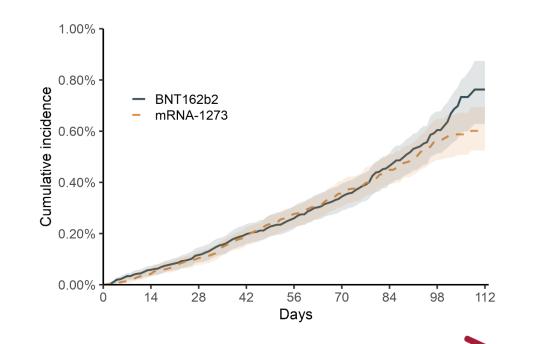
Negative control analyses suggested little confounding



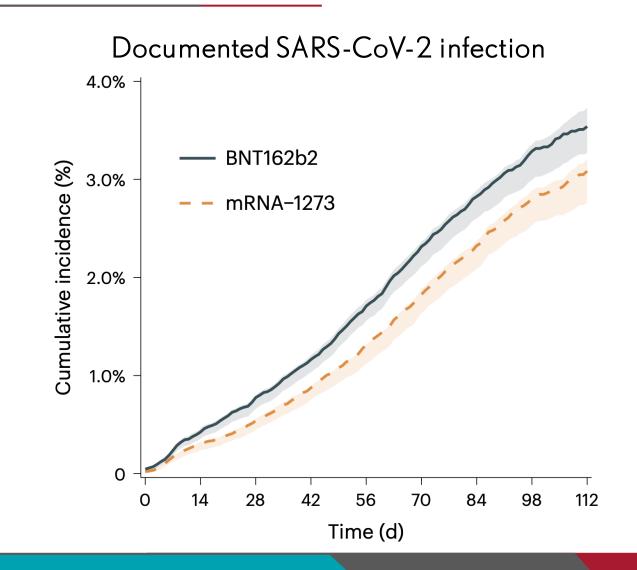
Negative control outcome #1: Symptomatic Covid-19 in the first 7 days after the third vaccine dose



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

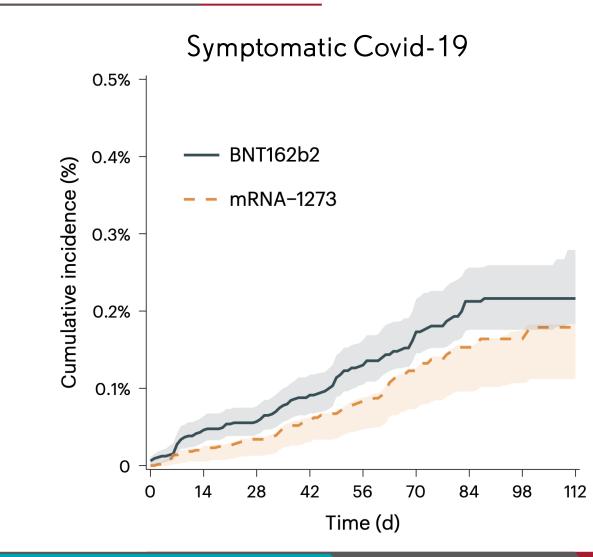




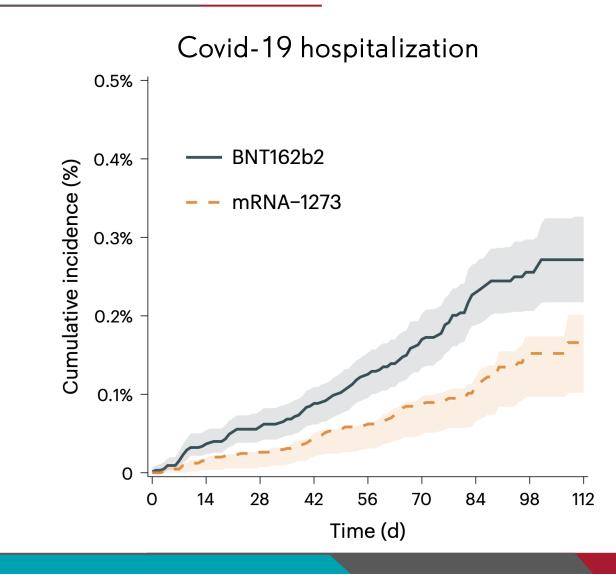




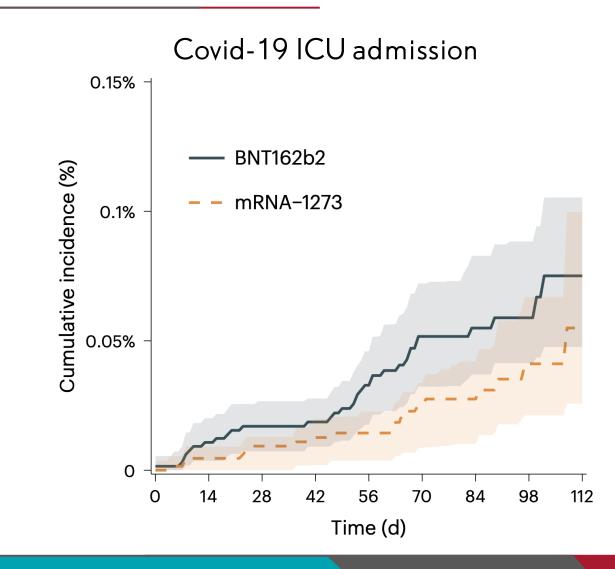




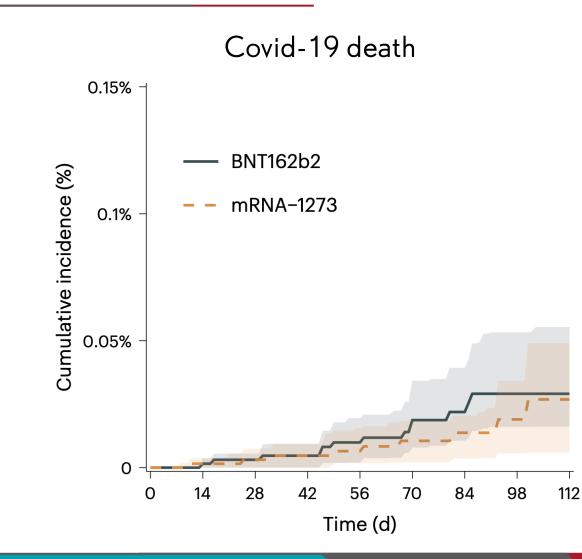






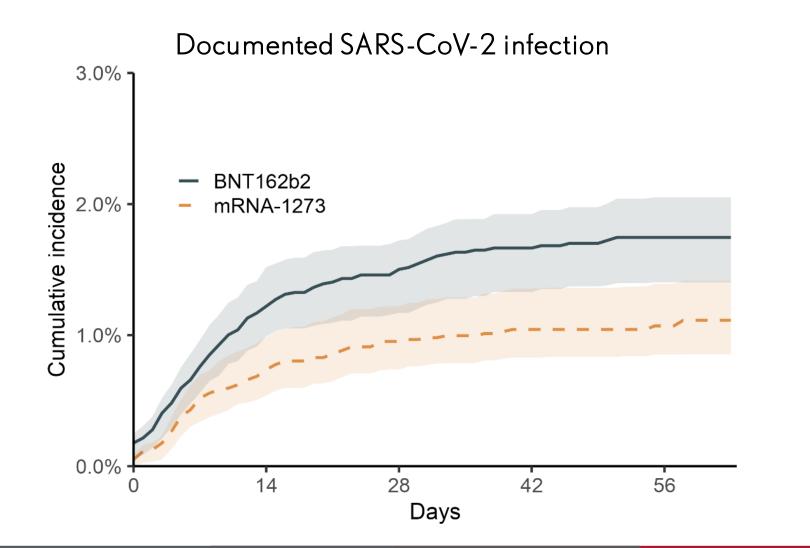






This pattern was similar in a time period restricted to omicron-variant predominance







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



FAQ How to Contribute Newsletter Partners Phenotyping Resources Data Visualization Tools Phenotype Entry Wizard Phenotype Catalogue Phenotyping Resource Library

VA CAUSAL Methods Core [edit]

2.2 Mental Health

VA CAUSAL is a scientific initiative aimed at enabling the VA to be a international leader in causal inference research across various health domains of importance to Veterans, including infectious disease, cancer, cardiovascular disease, and mental health. For each of these projects, the Methods Core carries out the development phase and the Implementation and Research Operations Core the dissemination and implementation phase.

Publications [edit]

COVID-19 [edit]

Partner Resources

Dickerman BA, Gerlovin H, Madenci AL, Kurgansky KE, Ferolito BR, Figueroa Muñiz MJ, Gagnon DR, Gaziano JM, Cho K, Casas JP, Hernán MA. Comparative Effectiveness of BNT162b2 and mRNA-1273 Vaccines in U.S. Veterans. N Engl J Med. 2022 Jan 13;386(2):105-115. doi: 10.1056/NEJMoa2115463. Epub 2021 Dec 1. PMID: 34942066; PMCID: PMC8693691. PubMed Article Analytic Code and Materials

Dickerman BA, Madenci AL, Gerlovin H, Kurgansky KE, Wise JK, Figueroa Muñiz MJ, Ferolito BR, Gagnon DR, Gaziano JM, Cho K, Casas JP, Hernán MA. Comparative Safety of BNT162b2 and mRNA-1273 Vaccines in a Nationwide Cohort of US Veterans. JAMA Intern Med. 2022 Jul 1;182(7):739-746. doi: 10.1001/jamainternmed.2022.2109. PMID: 35696161; PMCID: PMC9194743. PubMed Article 🗗

Dickerman BA, Gerlovin H, Madenci AL, Figueroa Muñiz MJ, Wise JK, Adhikari N, Ferolito BR, Kurgansky KE, Gagnon DR, Cho K, Casas JP, Hernán MA. Comparative effectiveness of third doses of mRNA-based COVID-19 vaccines in US veterans. Nat Microbiol. 2023 Jan;8(1):55-63. doi: 10.1038/s41564-022-01272-z. Epub 2023 Jan 2. PMID: 36593297; PMCID: PMC9949349. PubMed Article Analytic Code and Materials





 Centralized Interactive Phenomics Resource (CIPHER)

- Partners Pages
 <u>VA CAUSAL</u>
 <u>VA CAUSAL Methods Core</u>
- **N** Publications and materials



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

GitHub and General Architecture



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Starting Point



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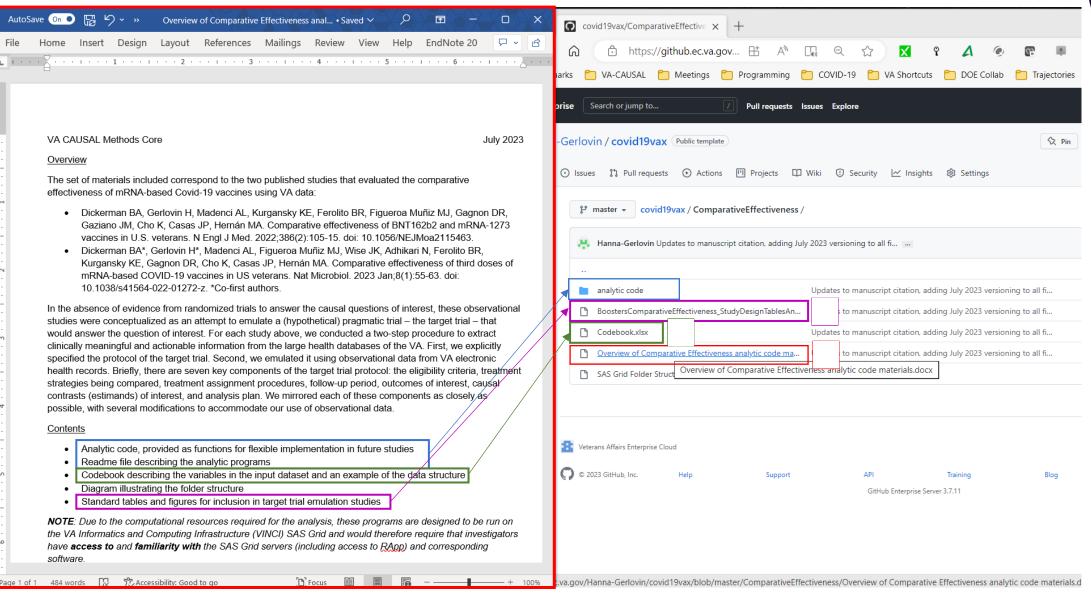
Overview of Materials



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	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:	The set of materials included correspond to two published studies that evaluated the comparative effectiveness of mRNA-based Covid-19 vaccines using VA data:
	 Dickerman BA, Gerlovin H, Madenci AL, Kurgansky KE, Ferolito BR, Figueroa Muñiz MJ, Gagnon DR, Gaziano JM, Cho K, Casas JP, Hernán MA. Comparative effectiveness of BNT162b2 and mRNA-1273 vaccines in U.S. veterans. N Engl J Med. 2022;386(2):105-15. doi: 10.1056/NEJMoa2115463. Dickerman BA*, Gerlovin H*, Madenci AL, Figueroa Muñiz MJ, Wise JK, Adhikari N, Ferolito BR, Kurgansky KE, Gagnon DR, Cho K, Casas JP, Hernán MA. Comparative effectiveness of third doses of mRNA-based COVID-19 vaccines in US veterans. Nat Microbiol. 2023 Jan;8(1):55-63. doi: 10.1038/s41564-022-01272-z. *Co-first authors. 	 Dickerman BA, Gerlovin H, Madenci AL, Kurgansky KE, Ferolito BR, Figueroa Muñiz MJ, Gagnon DR, Gaziano JM, Cho K, Casas JP, Hernán MA. Comparative effectiveness of BNT162b2 and mRNA-1273 vaccines in U.S.veterans. N Engl J Med. 2022;386(2):105-15. doi: 10.1056/NEJMoa2115463. Dickerman BA*, Gerlovin H*, Madenci AL, Figueroa Muñiz MJ, Wise JK, Adhikari N, Ferolito BR, Kurgansky KE, Gagnon DR, Cho K, Casas JP, Hernán MA. Comparative effectiveness of third doses of mRNA-based COVID-19 vaccines in US veterans. Nat Microbiol. 2023 Jan;8(1):55-63. doi: 10.1038/s41564-022-01272-z. *Co-first authors.
	In the absence of evidence from randomized trials to answer the causal questions of interest, these observational studies were conceptualized as an attempt to emulate a (hypothetical) pragmatic trial – the target trial – that would answer the question of interest. For each study above, we conducted a two-step procedure to extract clinically meaningful and actionable information from the large health databases of the VA. First, we explicitly specified the protocol of the target trial. Second, we emulated it using observational data from VA electronic health records. Briefly, there are seven key components of the target trial protocol: the eligibility criteria, treatment strategies being compared, treatment assignment procedures, follow-up period, outcomes of interest, causal contrasts (estimands) of interest, and analysis plan. We mirrored each of these components as closely as possible, with several modifications to accommodate our use of observational data.	In the absence of evidence from randomized trials to answer the causal questions of interest, these observational studies were conceptualized as an attempt to emulate a (hypothetical) pragmatic trial – the target trial – that would answer the question of interest. For each study above, we conducted a two-step procedure to extract clinically meaningful and actionable information from the large health databases of the VA. First, we explicitly specified the protocol of the target trial. Second, we emulated it using observational data from VA electronic health records. Briefly, there are seven key components of the target trial protocol: the eligibility criteria, treatment strategies being compared, treatment assignment procedures, follow-up period, outcomes of interest, causal contrasts (estimands) of interest, and analysis plan. We mirrored each of these components as closely as possible, with several modifications to accommodate our use of observational data.
	 Analytic code, provided as functions for flexible implementation in future studies Readme file describing the analytic programs 	Contents
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	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 <u>RApp</u>) and corresponding	Diagram illustrating the folder structure
● ge 1 of 1	Software. Who may find this set of materials useful? 484 words	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.









Study Design Tables and Figures

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Hanna-Gerlovin Updates to manuscript citation, adding Ju 3 hours ago 🕚	*Dr. Dickerman and Dr. Gerlovin contributed equally. Affiliations: ¹ CAUSALab. Harvard T.H. Chan School of Public Health, Bo ² Department of Epidemiology, Harvard T.H. Chan School of I			
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VA-CAUSAL Methods Core

July 2023

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
component 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 at hird 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: Severe allergic reaction (e.g., anaphylaxis) or immediate reaction of any severity to the vaccine or any of its components 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 inperson or telehealth primary care visit in the past year) Known smoking status and known body mass index in the past year 	 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	 Receive a third dose of BNT162b2 vaccine at baseline, or 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 <i>Immunization</i> domain and procedures recorded in the <i>Outpatient</i> or <i>Inpatient</i> domains.

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Treatment

Outcomes

Follow-up

Causal

contrasts

Statistical

analysis

Individuals are randomly assigned to a strategy at We assumed random assignment after assignment baseline within strata defined by calendar date of third matching eligible individuals who received dose (5-day bins), calendar month of second dose a third dose of the BNT162b2 vaccine in a (exact), age (5-year bins), sex (male, female), race 1:1 ratio to eligible individuals who (white, black, other, unknown), urbanicity of residence received a third dose of the mRNA-1273 (urban, not urban), geographic location coded as 19 vaccine, using the same factors used for stratified randomization as in the target categories of Veterans Integrated Services Network, and number of SARS-CoV-2 tests performed in the trial. past 12 months (0, 1, ≥2). Individuals will be aware of the assigned treatment strategy. Same as for the target trial. We identified Documented SARS-CoV-2 infection incident SARS-CoV-2 infections using the Symptomatic Covid-19 (defined as ≥1 of the VA Covid-19 National Surveillance Tool, following symptoms within 4 days of SARS-CoV-2 described above. We assessed symptoms infection): fever, chills, cough, shortness of breath using records in the Outpatient, Inpatient, or difficulty breathing, sore throat, loss of taste or Vital Signs, Health Factors, and Fee smell, headache, myalgia, diarrhea, vomiting domains. We assessed VA Hospitalization due to Covid-19 hospitalizations using records in the ICU admission due to Covid-19 Inpatient domain, ICU admissions using · Death due to Covid-19 (defined as death within 30 records in the Inpatient domain and days of SARS-CoV-2 infection) specialty transfer codes, and deaths using records in the Patient domain. For each person, follow-up starts on the day the third Same as for the target trial. 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. Intention-to-treat effect. Observational analogue of the perprotocol effect. Per-protocol effect, i.e., the effect if all individuals had received the vaccination they were assigned to receive at baseline. Cumulative incidence (risk) curves and estimates of Same as for the target trial, except we 16-week risk, risk differences, and risk ratios were unable to conduct subgroup comparing the vaccination groups. analyses by previously documented SARS-CoV-2 infection (yes or no) due to Subgroup analyses by baseline age, race, time since lack of variability in the data. 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.

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

BoostersComparativeEffectiveness StudyDesignTablesAndFlowchart.docx



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July 2023



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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
			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	Outpatient codes:
oymptomate oond to	maioator	100/100	symptoms documented within	ICD10: A68.9, B33.0.
			the VA health care system	M79.1, M79.10, M79.11
			within 4 days after	M79.12, M79.18, R05.
			documented SARS-CoV-2	R06.00, R06.01, R06.02,
			infection: fever, chills, cough,	R06.03, R06.09, R07.0,
			shortness of breath or	R09.3, R43.0, R43.2
			difficulty breathing, sore	R43.8, R43.9, R50.2
			throat, loss of taste or smell,	R50.81, R50.82, R50.83
			headache, myalgia, diarrhea,	R50.84, R50.9, R56.00
			vomiting.	R56.01, R68.83
			The event date is the	
			specimen collection date.	
			Based on records in the	
			Outpatient, Inpatient, Vital	
			Signs, Health Factors, and	
			Fee domains.	
Hospitalization due to	Indicator	Yes/No	Defined as a hospitalization	N/A
Covid-19			within 21 days after	
			documented SARS-CoV-2	
			infection. Based on records in	
			the Inpatient domain. The	
			event date is the hospital	
	1		admission date.	

BoostersComparativeEffectiveness_StudyDesignTablesAndFlowchart.docx

11

BoostersComparativeEffectiveness_StudyDesignTablesAndFlowchart.docx

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

Values

Yes/No

Yes/No

VA-CAUSAL Methods Core

Administration Electronic Health Records.

Functional

Indicator

Indicator

Indicator

Indicator

Indicator

form

Variable

Dementia

Substance use disorder

Time-varying BNT162b2 vaccination

mRNA-1273

vaccination

Documented infection

coronavirus 2 (SARS-

with severe acute respiratory syndrome

CoV-2)

12

28

July 2023



July 2023

ICD10: F00%, F01%,

G30%, G31.1%

F02%, F03%, F05.1%,

ICD10: F10.10, F10.11

F11.11, F11.12%, F11.14, F11.15%, F11.18% F11.19, F11.2%, F11.9%

F10.12%, F10.14

F10.15%, F10.18% F10.19, F10.2%, F11.10,

CPT: 0001A, 0002A,

91300, 91305

CVX: 208, 217

0004A, 0054A Booster Immunization Series: "B"

91306

N/A

CVX: 207

0064A, 91306

0003A. 0004A. 0051A. 0052A, 0053A, 0054A,

Booster-specific CPT

CPT: 0011A. 0012A.

0013A, 0064A, 91301

Booster-specific CPT

Boosters Immunization Series: "B"

Codes

Detail

Defined as ≥2 diagnoses in the past 2 years. Based on

Outpatient, and Fee domains.

Defined as ≥2 diagnoses in

the past 2 years. Based on records in the Inpatient.

Outpatient, and Fee domains.

the Immunization domain and

identified by procedure codes

the Immunization domain and

procedures recorded in the

identified by procedure codes

swab, nasal swab, or saliva

Outpatient or Inpatient

or series designation.

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

domains. Booster doses

procedures recorded in the Outpatient or Inpatient

domains. Booster doses

or series designation.

Yes/No Defined using records in both

Yes/No Defined using records in both

Yes/No Defined as a nasopharyngeal

records in the Inpatient,

Standardizing Study Design Elements

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

VA-CAUSAL Methods Core July 2023 Figure 1. Flowchart Selection of Persons for the Emulation of a Target Trial Evaluating the Comparative Effectiveness of a Third Dose of BNT162b2 and mRNA-1273 Vaccines during a Period Spanning Delta- and Omicron-Variant Predominance (October 20, 2021–February 15, 2022). VA denotes Department of Veterans Affairs. 3,175,771 Veterans ≥65 yr of age or 18-64 years of age with high risk of severe Covid-19 between October 20, 2021, and November 18, 2021, or ≥18 yr of age between November 19, 2021, and February 8, 2022, with documented receipt of the second dose of an mRNA Covid-19 vaccine at least 6 months earlier, were identified in the VA database 1.170.681 Received a third Had an interaction with the health care dose of BNT 162b2 or mRNAsystem within 3 days before the vaccination 1273 before February 8, 2022 d ate (39,382) Did not have a known residential address or were in long-termcare (28,735) Were not determined to be a user of the VA health care system in the past year (26,403) Did not have recentd ata on body mass indexorsmoking (392,102) Had an incomplete Covid-19 vaccination record (256,429) 427,630 Were evaluated for inclusion in the study 170.748 Received a 256.882 received a BNT162b2 third dose mRNA-1273 third dose 147,553 Attended a VA 214,728 Attended a VA station that administered the station that administered the mRNA-1273 vaccine and BNT162b2 vaccine and were were eligible for subsequent eligible for subsequent analyses analyses 65, 196 Were included in the 65, 196 Were included in the 1.1 matched cohort matching matched cohort BoostersComparativeEffectiveness StudyDesignTablesAndFlowchart.docx 14





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	File Home Insert	Page Layout Formulas	Data Review View Help		
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	Α		В	С	D
	1 Codebook for va	- riables used in the an	alysis of studies of the compa	rative effectiveness of mRNA-based Covid-	19 vaccines
🕼 🔲 💽 covid19vax/ComparativeEffective 🗙 /+	2 Accompanying the foll				
	3 - Dickerman BA, Gerlov	in H, Madenci AL, Kurgansky K	E, Ferolito BR, Figueroa Muniz MJ, et al. Co	omparative effectiveness of BNT162b2 and mRNA-1273	
\leftarrow C \bigcirc https://githu \boxplus AV \heartsuit \circlearrowright	4 vaccines in U.S.veteran	s. N Engl J Med. 2022;386(2):1	05-15.		
	5 - Dickerman BA*, Gerlo	vin H*, Madenci AL, Figueroa	Muniz MJ, Wise JK, Adhikari N, et al. Comp	arative effectiveness of third doses of mRNA-based COVID	-
🎦 VA Bookmarks 📋 VA-CAUSAL 📋 Meetings 🛛 💦 🔪		ans. Nat Microbiol. 2023 Jan;8			
	7 NOTE:			nis case, days]). The trajectory for each individual starts on	
	8			or the outcome of interest, death, or the administrative end	
P master - covid19vax / Comparative Effectiveness /	9			arious mechanisms may instead end an individual's	
	0		the outcome of interest, censoring, death	, or the administrative end of follow-up.	
	1 Author(s):	VA-CAUSAL Methods Core			
🕂 Hanna-Gerlovin Updates to manuscript citation, adding Ju 📖 3 hour	2 Contact Information:	-		ture, questions about the implementation of these	
	3 4 Marrian		the VA-CAUSAL Implementation and Rese	arch Operations Core (contact information coming soon).	
	4 Version	July 2023			
	5 6 Codebook Tab Informa	ation			
analytic code	7 Codebook Column	Description			
	8 Variable Name		ld appear in the dataset being used with th	ne programs	
1 BoostersComparativeEffectiveness StudyDesignTablesAndFlowchart.docx	9 Definition	Description of the variable	a appear in the dataset being used with th		
	0 Code or Value	Numeric, categorical values			
Codebook.xlsx	1 Value Description	Formats for the values			
Overview of Comparative Effectiveness analytic code materials.docx	2				
	3 ExampleLong Tab Info	rmation			
SAS Grid Folder Structure.pdf			r one hypothetical individual that might be	included in these analyses. Each row represents a differer	ıt
	5 person-day, and each c	olumn represents a different f	eature (baseline or time-varying). Each inc	lividual's record extends from baseline through the soones	t
	6 of the outcome of inter	rest, death, or administrative e	nd of follow-up. This tab provides exampl	es of records truncated upon the outcomes of Covid-19	
	27 death and of any docum	nented SARS-CoV-2 infection,	to demonstrate the data inputs used in ea	ch respective analysis for this individual.	
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**** "Codebook" Tab

	Α	В	С	D	E	F		
1	1 Codebook for variables used in the analysis of studies of the comparative effectiveness of mRNA-based Covid-19 va							
2								
3	Variable Name	Definition 🗸	Code or Value 👻	Value Description 👻				
4	Age_at_index	Age (years) at baseline	Numeric	Continuous				
				18-39, 40-49, 50-59, 60-				
5	age_cat	Age (categorical) at baseline	0, 1, 2, 3, 4, 5	69, 70-79, <mark>8</mark> 0+				
6	BMI	Body Mass Index (kg/m²) 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

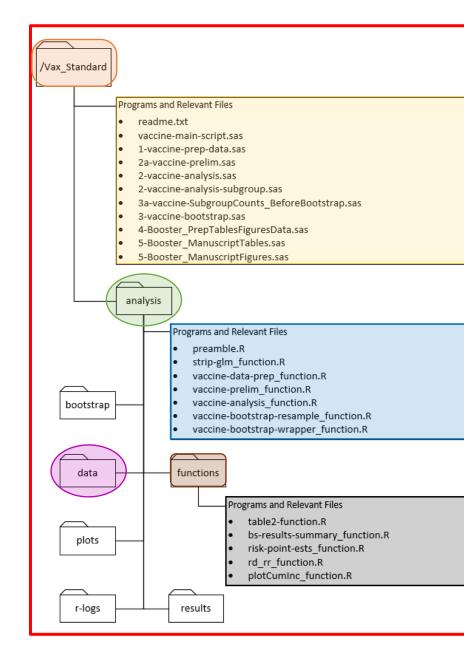
	А	В	С	D	E	F	G	Н	1	J	к	L	М	N	0	Р	Q	R
1	newid	caldate	age_at_index	dose3_dt	eligible_PM	keep_PM	ΡvΜ	covidpos	firstpos_dt	COVIDdeath	covid_dateofdeath	death	noncoviddeath	dateofdeath				
2	1	1/1/2022	57	1/4/2022	0	0	1	0	1/11/2022	0	1/13/2022	2 () (1/13/2022				
3	1	1/2/2022	57	1/4/2022	0	0	1	0	1/11/2022	0	1/13/2022	2 () (1/13/2022				
4	1	1/3/2022	57	1/4/2022	0	0	1	0	1/11/2022	0	1/13/2022	2 () (1/13/2022				
5	1	1/4/2022	57	1/4/2022	1	1	1	0	1/11/2022	0	1/13/2022	2 () (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	2 () (1/13/2022				
7	1	1/6/2022	57	1/4/2022	0	1	1	0	1/11/2022	0	1/13/2022	2 () (1/13/2022				
8	1	1/7/2022	57	1/4/2022	0	1	1	0	1/11/2022	0	1/13/2022	2 () (1/13/2022				
9	1	1/8/2022	57	1/4/2022	0	1	1	0	1/11/2022	0	1/13/2022	2 () (1/13/2022				
10	1	1/9/2022	57	1/4/2022	0	1	1	0	1/11/2022	0	1/13/2022	2 () (1/13/2022				
11	1	1/10/2022	57	1/4/2022	0	1	1	0	1/11/2022	0	1/13/2022	2 () (1/13/2022				
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Disclaimer About Analytic Programs

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Diagram Illustrating the Folder Structure



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Navigating the readme and scripts

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💭 covid19vax/ComparativeEffective 🗙

🗅 https://github.ec.va.gov/Hanna-Gerlovin/covid19vax/tree/master/ComparativeEffectiv... 🗄 A^N 52 G 6 🎦 VA-CAUSAL 🎦 Meetings 🎦 Programming 🎦 COVID-19 🎦 VA Shortcuts 🎦 DOE Collab 🦰 Trajectories 🎦 Useful Seminars 🎦 Career 🎦 Bookmarks bar 🤷 VA CAUSAL Metho... marks Ø

readme.txt

/*

This is a README outlining the analytic programs used to evaluate the comparative effectiveness of mRNA-based Covid-19 vaccines in the following manuscripts: - 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.

It is assumed that the input dataset for these programs contains all necessary analytic variables, as described in the accompanying codebook. Certain programs in this package are flexible enough to accommodate applications with different goals (e.g., comparative effectiveness of primary series, third doses); our examples for their invocations focus on one potential application (comparative effectiveness of third doses) for simplicity.

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

*/

ANALYSIS ******

"vaccine-main-script.sas" is a single script to

1) prepare data,

2) (a) run negative control analyses and other preliminaries, (b) generate point estimates

3) (a) check counts then (b) perform bootstrap resample,

4) prepare summary data for tables and figures

and (5) generate confidence intervals, Kaplan-Meier plots, and Manuscript tables

Across the inner R programs, the following arguments persist:

- "treat" (e.g., PvM, MvP)

- "event" (e.g., covidpos, covidpossymp, covidhosp, covidICU, COVIDdeath, notcoviddeath)

- "method" takes either "exact" (N:N exact matching) or "cem" (coarsened exact matching)

- "variant" is used to specify the four different time-period analyses included. This is used for naming outputted logs, reading in cleaned datasets, naming saved matched data, naming negative control KM plot, and assigning default values for the inner scripts. Possible values are "alpha", "delta", "delom booster", and "omicron boost"

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

Teadme.txt - Notepad - X	🧾 vaccine-main-script_boosters.sas - Notepad —	K 🗐 2a-vaccine-prelim.sas - Notepad — 🗆 🗙 🙀
<u>F</u> ile <u>E</u> dit F <u>o</u> rmat <u>V</u> iew <u>H</u> elp	Eile Edit Format View Help	Eile Edit Format View Help
<u>File Edit Format View Help</u> 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.	<pre>/************************************</pre>	<pre>/* 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 BNTI62b2 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:</pre>
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 	<pre>%Iet event4 = covidICU; %Iet event5 = COVIDdeath; %Iet event5 = otcoviddeath; %macro prelim(treat, variant); % do i=1 %to 6; %mygsub(jobname=vaccine_prelim</pre>	<pre>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="alpha" then do; risktime = 63; daysfu = 7; end; else if variant1="alpha" then do; risktime = 168; daysfu = 7; end; else if variant1="delta" then do; risktime = 83; daysfu = 10; end; %put risktime; %put daysfu; submit event1treat1variant1 risktime daysfu/ R;</pre>
log file. 2b. macro "point_est" runs script "2-vaccine-analysis.sas" (which calls "vaccine-analysis_function.R") on the server	<pre>/*%prelim(treat=MvP,variant=delom_booster); *alternative contrast approach;*/ /**********************************</pre>	<pre>event <- "&event1" treat <- "&treat1" variant <- "&variant1" risk_time <- "&risktime" days_fu <- "&daysfu" source("[SAS folder ORD Project]/Vax Standard/analysis/preamble.R", echo=TRUE)</pre>
<pre>- 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-</pre>	<pre>/************************************</pre>	<pre>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") <- c("Age_at_index + sex + race + VISN + Caldate_num + urbanicity } 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",</pre>
<pre>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:</pre>	<pre>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);</pre>	<pre>risk_time-as.numeric(risk_time), matching.formula = paste0("group.binary ~ ",matchform), variant = variant quit;</pre>
	/*%point est(treat=MvP,variant=delom booster); *alternative contrast approach;*/	Ln 34. Col 23 70% Unix (LF) UTF-8

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



R code within SAS Grid*

Example: prelim_function()

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4 – perform matching with pre-specified seed covid19vax / ComparativeEffectiveness / analytic code / analysis / vaccine-prelim_function.R 37 # Perform matching to allow for preliminary checks 115 # Check the Kaplan-Meier curves for first 7-10 days (negative control, no ex 38 if(method=="exact"){ 116 km.data <- survfit(Surv(days, outcome) ~ group.binary, data=m.out %>% 39 set.seed(5) 117 mutate(group.binary = factor(group.binary)) %>% 💾 Hanna-Gerlovin Updates to manuscript citation, adding July 2023 versioning t... 📖 (1) History 40 m.out <- match.data(matchit(formula = as.formula(matching.formula),</pre> 118 mutate(group.binary = forcats::fct_relevel(group.binary 41 data=fread(file=paste0(prefix, "/data/cleaned-119 42 filter(!is.na(Age_at_index)), # removed n=2 120 mypal=ggsci::pal_jama("default",alpha=1)(2) As 1 contributor 43 method="exact", 121 44 122 verbose=TRUE, #progress bar neg.control.km.plot <- suppressWarnings(survminer::ggsurvplot(km.data, data=</pre> 45 k2k=TRUE))[,.(newid, group.binary, outcome, ne 123 palette = c(mypal[1 8 – build the negative control plot 157 lines (137 sloc) 9.45 KB 124 46 n_1 <- unique(m.out[group.binary==1,][,num_1 := .N, by=.(subclass)][, .(subclass)]</pre> size=1. 47 n_0 <- unique(m.out[group.binary==0][, num_0 := .N, by=.(subclass)][, .(su</pre> 125 censor=FALSE. 1 ##### 48 n <- n_1[n_0, on=.(subclass)][, num := pmin(num_1, num_0)][]</pre> 126 fun="event", 49 m.out.num <- n[m.out, on = .(subclass)][]</pre> 127 linetype=c(1,2), 3 # This script is a part of a set of analytic programs related to the following manuscript(s): 50 m.out <- rbindlist(list(m.out.num[group.binary==0,][, .SD[sample(x=.N, siz</pre> 128 font.main=24. - Dickerman BA, Gerlovin H, Madenci AL, Kurgansky KE, Ferolito BR, Figueroa Muniz MJ, et al. 51 m.out.num[group.binary==1,][, .SD[sample(x=.N, siz 129 legend=c(0.12, 0.8 Dickerman BA*, Gerlovin H*, Madenci AL, Figueroa Muniz MJ, Wise JK, Adhikari N, et al. Compa 52 130 legend.title="", 53 if(method=="cem"){ 131 legend.labs=c(paste 7 # Author(s): VA-CAUSAL Methods Core 54 set.seed(5) 132 risk.table=TRUE, 8 # Version: July 2023. 55 133 risk.table.height 56 if(variant %in% c("alpha","delta")) { 134 tables.y.text.col=F 1 - setup the function and defaults ###### 57 m.out <- match.data(matchit(formula = as.formula(matching.formul</pre> 135 fontsize=10, data=fread(file=paste0(prefix, "/data/cleaned-136 xlim=c(0,days_fu), prelim_function <- function(event="covidpos", treat="PvM", days_fu=7, risk_time=168,</pre> 137 break.x.bv=1. method=c("exact", "cem"), 88 138 xlab="Days", matching.formula = paste0("group.binary ~ Age_at_index + sex + race print("matching done") 89 139 ylim=c(0,0.005), number.rows=Inf, variant="alpha" 90 5 – save the matched data for use in tables 140 surv.scale="percent 2 - load program dependencies 91 141 ylab="Cumulative in # May want to uncomment the bracketed lines to not save the datasets for 92 142 ggtheme=theme survn # Load the server/path specifications for the R session 93 #if(event=="covidpos"){ 143 preamble(...); source(paste0(prefix, "/strip-glm_function.R")) 94 fwrite(m.out[,.(newid, group.binary, outcome, newperiod, subclas 144 95 file=paste0(prefix, "/data/matched-dat-",treat,"-",event,"-",met 145 # Initialize an r-log 3 - initialize the logs 96 #} if(server){ 97 6 – print event counts and preliminary statistics to log my_log <<- file(paste0(prefix, "/r-logs/log-vaccine-prelim-", treat, "-", event,"-",method,"</pre> 98 sink(my_log, append=TRUE) 99 # Save descriptives to log for preliminary checks 149 tables.theme=theme sink(my_log, append=TRUE, type="message") 100 9 – save the PDF plot print(paste("Matched data, number of treat1 for", treat, "comparison:", table(m.c 150 101 print(paste("Matched data, number of treat0 for", treat, "comparison:", table(m.c 151 102 print(paste("Matched data, number of events, total:",table(m.out\$outcome[m.out 152 #save negative control KM plot (pdf) print(variant) 103 print(paste("Matched data, number of events, in treat1:",table(m.out\$outcome[n 153 pdf(paste0(prefix,"/plots/figure-neg-control-km-plot_",treat,"-",event,"-",m 104 print(paste("Matched data, number of events, in treat0:",table(m.out\$outcome[m 154 print(neg.control.km.plot,newpage=FALSE) #define legend labels based on supplied treat variable 105 print(paste("Matched data, follow-up time, median:",quantile(pmin(m.out\$days,r 155 dev.off() legend_treat1 <- fcase(treat=="PvM","BNT162b2",</pre> 106 print(paste("Matched data, follow-up time, 25th percentile:",quantile(pmin(m.d 156 treat=="MvP","mRNA-1273") 107 print(paste("Matched data, follow-up time, 75th percentile:",quantile(pmin(m.c 157 } print(paste("Matched data (treat=1), follow-up time, median:".guantile(pmin(m 108

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

Who may find this set of materials useful?



- > Point interventions (administered at a single point in time)
- Saseline 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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- MVP Data Core

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