R Supplement for 'Evaluation of Test-Negative Designs with Randomized Placebo-Controlled Trials'

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This R Supplement provides the code to perform the analyses from the manuscript, "COVID-19 Vaccine Effectiveness: An Evaluation of the Test-Negative Design with Randomized Placebo-Controlled Clinical Trials." The manuscript resamples data from five Phase 3 COVID-19 Prevention Network (CoVPN) Randomized Placebo-Controlled Trials (RCTs) using several test-negative design (TND) sampling approaches and applies a novel semiparametric logistic regression approach involving targeted maximum likelihood estimation to estimate vaccine effectiveness.

The CoVPN RCT data cannot be shared so instead, we generated a toy RCT dataset to illustrate how we conducted the analyses. We applied four common TND sampling methods to the toy RCT dataset to obtain four TND samples: participant-based sample without censoring for COVID-19, participant-based sample with censoring for COVID-19, specimen-based sample, and random specimen-based sample. We then applied the semiparametric logistic regression involving targeted maximum likelihood estimation and an ordinary logistic regression approach, as described in the manuscript, to each TND sample to estimate TND vaccine effectiveness against symptomatic virologically-confirmed COVID-19. We also estimated RCT vaccine efficacy using an unadjusted Cox Proportional Hazards Regression model on the entire RCT cohort for comparison.

Generating Data

Since we cannot share the CoVPN RCT data, we generate a toy phase 3 COVID-19 RCT cohort and obtain four TND samples from this cohort. We also define a non-SARS-CoV-2 endpoint, defined as meeting the COVID-19 symptom definition and testing SARS-CoV-2 negative, in the RCT cohort to mimic our analyses in the manuscript that assess Noncase Exchangeability violations.

RCT Cohort

Our toy RCT dataset consists of 30,000 participants who are randomly assigned to receive one dose of the COVID-19 vaccine or placebo at a 1:1 ratio. The blinded phase of the RCT takes place from August 1, 2020 to March 31, 2021. For simplicity, all participants are vaccinated in the first two weeks of August and no participants are unblinded early or lost to follow up. At RCT enrollment, age, sex at birth, race/ethnicity, geographic region, and presence of any comorbidities were measured for all participants. There is no missing data on any covariates.

```
## Demographic and Clinical Characteristics
# One Row per Participant
set.seed(7)
nsubj <- 30000

demo.df0 <- data.frame(USUBJID = paste0("ID", 1:nsubj),
                       AGE = round(runif(nsubj, min = 18, max = 80)),
```

```
                 SEX = sample(c("F", "M"), nsubj, replace = TRUE),
                 # Dichotomized Race/Ethnicity (Hispanic/Latino or Non-White vs.
                 # Non-Hispanic/Non-Latino White)
                 POC = sample(c("POC", "White"), nsubj,
                              replace = TRUE, prob = c(1/3, 2/3)),
                # US Census Regions
                 REGION = sample(c("Midwest", "NE", "South", "West"), nsubj,
                                 replace = TRUE, prob = c(2/10, 1/10, 5/10, 2/10)),
                # Presence of Comorbidities
                 COMORB = sample(c("Comorbidities", "No Comorbidities"), nsubj,
                                 replace = TRUE, prob = c(1/4, 3/4)),
                # Intervention Date (Placebo or Vaccine)
                DOSE2DT = sample(seq(as.Date('2020/08/01'), as.Date('2020/08/14'), by="day"),
                                 nsubj, replace = TRUE),
                # Randomized Vaccination Status
                VACCINE = sample(0:1, nsubj, replace = TRUE),
                # End of Blinded Phase Date
                ENDDT = as.Date('2021/03/31'))
```

During the RCT, participants may experience an illness episode or symptomatic period and are then prompted to seek SARS-CoV-2 testing. In this dataset, participants can experience 0-5 illness episodes during the study and the date of any symptom onset (`ONSETDT`) and first date of meeting the COVID-19 like symptom definition (`SYMDT`) are documented. By definition, the date of meeting the symptom definition must occur on or after date of symptom onset. Illness episodes may be truly caused by SARS-CoV-2 or by a non-SARS-CoV-2 illness (e.g., other respiratory viruses or allergies). By construction, the COVID-19 vaccine protects against COVID-19 (vaccine efficacy = 80%) and does not affect non-SARS-CoV-2 illness.

Participants obtain 1-10 SARS-CoV-2 PCR tests before and/or during an illness episode. While an illness episode may be truly caused by SARS-CoV-2 (`eps_sars_inf=1`), SARS-CoV-2 test results (`POSTEST`) are subject to misclassification (100% specificity, 85% sensitivity). Thus, the unobserved true SARS-CoV-2 infection status of an illness episode, `eps_sars_inf`, does not always match the observed SARS-CoV-2 test results from an illness episode, `POSTEST`.

```
# Adding Illness Episode Information
demo.df <- demo.df0 %>% mutate(
     # True SARS-CoV-2 Infection Status at Any Point during Blinded Phase
     # (Unknown in Observed Clinical Data)
     # Vaccine Protects Against SARS-CoV-2 Infection
      any_sars_inf = rbinom(nrow(.), 1, exp( log(0.04) + log(0.2)*VACCINE) ),
      # Number of SARS-CoV-2 Illness Episodes
      n_sars_eps = any_sars_inf*sample(1:2, nsubj, replace=  TRUE, prob = c(0.95, 0.05)),
      # Number of Non-SARS-CoV-2 Illness Episodes
      n_nonsars_eps = sample(0:3, nsubj, replace = TRUE, prob = c(0.9, 0.07, 0.02, 0.01)))


## Illness Episode Characteristics
# Creating One Row Per Illness Episode

# SARS-CoV-2 Illness Episodes
sars.eps.df0 <- uncount(demo.df , n_sars_eps) %>%
  # Illness Episode SARS-CoV-2 Infection Status
  mutate(eps_sars_inf = 1) %>% select(-n_nonsars_eps)

# Non-SARS-CoV-2 Illness Episodes
```

```r
non.sars.eps.df0 <- uncount(demo.df , n_nonsars_eps) %>%
  # Illness Episode SARS-CoV-2 Infection Status
  mutate(eps_sars_inf = 0) %>% select(-n_sars_eps)

# Adding Testing and Symptom Information for Both Types of Illness Episodes
eps.df00 <- rbind(sars.eps.df0, non.sars.eps.df0) %>% arrange(USUBJID)
eps.df0 <- eps.df00   %>% mutate(
              # Number of SARS-CoV-2 Tests within an Illness Episode
              ntests = sample(1:10, nrow(.), replace = TRUE),
              # Date of Symptom Onset Beginning of Illness Episode)
              ONSETDT = sample(seq(as.Date('2020/09/01'), as.Date('2021/03/31'),
                               by="day"), nrow(.), replace = TRUE),
              # Date of Meeting the COVID-19 Symptom Definition
              # For Simplicity, All Illness Episodes Meet the Symptom Definition
              # But This is Not a Requirement
              SYMDT = ONSETDT + sample(0:5, n(), replace = TRUE))%>%
                arrange(USUBJID, ONSETDT)
eps.df <- eps.df0 %>% group_by(USUBJID) %>% arrange(ONSETDT) %>%
  # Label Illness Episodes in Chronological Order
  mutate(EPISODE = 1:n()) %>% arrange(USUBJID)


## Testing Characteristics
# Creating One Row per SARS-CoV-2 Test Result
test.df0 <- uncount(eps.df, ntests)
test.df <- test.df0 %>% group_by(USUBJID)%>% mutate(
  # Test Date
  TESTDT = ONSETDT + sample(-3:15, n(), replace = TRUE),
  # Test Result Roughly Based on SARS-CoV-2 PCR Sensitivity and Specificity
  # 1 = positive, 0 = negative
  POSTEST = eps_sars_inf*rbinom(n(), 1, 0.85)) %>%
  # Only Include Tests while Blinded
  filter(TESTDT <= as.Date('2021/03/31'))
```

We use the demographic and testing data to identify RCT COVID-19 cases (`RCTCASE=1`), or participants who meet the COVID-19 symptom definition and obtain a SARS-CoV-2 positive test at least 14 days after vaccination. For this RCT, these criteria can be met in either order as long as both dates are within 15 days apart. The remaining RCT participants were right-censored at the end of the blinded phase.

```r
## Creating RCT Analysis Dataset

# Identify First SARS-CoV-2 Positive Test from RCT COVID Cases
# (In this Example Dataset, All Illness Episodes Met the Symptom Definition)
rct.case.df <- test.df %>%
  # Only take those who test SARS-CoV-2 Positive
  filter(POSTEST==1) %>% group_by(USUBJID)%>%
  slice_min(TESTDT, with_ties=FALSE)

# Adding COVID-19 Case's Testing Information to Demographic Information
rct.df0<- left_join(demo.df, rct.case.df[c("USUBJID","SYMDT","TESTDT","POSTEST")])
rct.df <- rct.df0 %>% rowwise() %>% mutate(
  # Endpoint Date: Unblinding Date or
  # Earliest Date of Meeting Symptom Definition and Positive Test
```

```
  RCTADT = if_else(is.na(POSTEST), ENDDT,min(SYMDT,TESTDT))) %>%
  ungroup()%>% mutate(
  # RCT COVID-19 Case Status
  RCTCASE= ifelse(is.na(POSTEST),0,1),
  # Time to COVID-19 or Censoring
  RCTTT = as.numeric(RCTADT-(DOSE2DT+14)+1))


# RCT Cases
rct_case_ids<- subset(rct.df, RCTCASE==1)$USUBJID

with(rct.df, table(VACCINE, RCTCASE))
```

```
##         RCTCASE
## VACCINE     0     1
##       0 14415   596
##       1 14872   117
```

From the RCT cohort of 30,000 participants, 713 participants were COVID-19 cases.

TND Samples

To create TND samples from RCT testing data, we only retain eligible SARS-CoV-2 tests, which must occur at least 14 days after final vaccination, within ten days after symptom onset, after meeting the symptom definition, and while blinded. In the TND analysis, we define illness episodes as symptomatic periods that last from symptom onset to at least 15 days after symptom onset and are separated by eligible SARS-CoV-2 tests that occur at least 30 days apart. We propose distinguishing illness episodes by eligible SARS-CoV-2 test dates rather than dates of symptom onset and resolution because symptom dates would be more difficult to recall and collect in a TND study. Since the illness episode variable `EPISODE` is defined differently in the RCT, we apply a stricter criteria to the existing RCT illness episode `EPISODE` variable. We define a positive episode as an illness episode that triggers at least one eligible SARS-CoV-2 positive test and a negative episode as an illness episode that does not trigger any SARS-CoV-2 positive tests and only triggers eligible SARS-CoV-2 negative tests.

```
# Only Retain TND Eligible Tests
tnd.test.df <- test.df %>% filter(  # Test At Least 14 Days After Vaccination
                                    TESTDT >= (DOSE2DT+14) &
                                    # Test within 10 Days After Symptom Onset
                                    TESTDT >= ONSETDT &
                                    TESTDT <= (ONSETDT +10) &
                                    # Test After Meeting the Symptom Definition
                                    TESTDT >= SYMDT &
                                    # Test While Blinded
                                    TESTDT <= ENDDT) %>%
            # Create Two Week Calendar Time Variable
            # Many TND Analyses Adjust for Categorical Calendar Time
            mutate(TWOWEEK0 = cut(TESTDT, "2 weeks"))

# Function that Identifies Tests That are at Least 30 days from Each Other
# Must be Applied to Data Grouped by Participant ID and Sorted by Testing Date
# Inputs:
#      col_vals: Values from a Date or Numeric Column
```

```
# Outputs: Boolean Vector, TRUE meaning rows are at least 30 days apart
#      First Value will Always be True
#
over30_func <- function(col_vals){
  # MUST BE USED AFTER GROUPED BY SUBJID AND SORTED BY DATE

  # starts with TRUE because have to keep first test
  empty_vec <- c(TRUE)
  nobs <- length(col_vals)
  if(nobs > 1){
    for(i in 1:(nobs-1)){
      # Are Two Tests at Least 30 Days Apart?
      val <- col_vals[i+1] - col_vals[i] >= 30
      empty_vec <- c(empty_vec, val)
    }
  }
  empty_vec
}
```

Specimen-Based Sample

The first TND sample we create is the specimen-based sample because all the other sampling methods require illness episodes defined using our TND definition. In the specimen-based sample, positive and negative episodes are defined as cases and noncases, respectively. Given low SARS-CoV-2 reinfection during the course of the RCT, participants only contribute their first positive episode and all negative episodes. The first positive or negative test is contributed from each positive or negative episode, respectively.

```
# Take One Test per RCT-Defined Illness Episode
# (Earliest Negative Test if All Negative Tests, or Earliest Positive Test)
spec.df0  <- tnd.test.df %>% group_by(USUBJID, EPISODE)%>%
  arrange(USUBJID, TESTDT) %>% slice(which.max(POSTEST))

# Only Retain Illness Episodes That Are at Least 30 Days Apart
spec.df01 <- spec.df0 %>% group_by(USUBJID) %>%
  arrange(TESTDT)%>% mutate(SEPILL = over30_func(TESTDT))
spec.df02 <- spec.df01 %>% filter(SEPILL==TRUE)

# Only Retain Earliest Positive Episode
spec.df <- spec.df02[!(duplicated(spec.df02[c("USUBJID", "POSTEST")]) &
                                        spec.df02$POSTEST==1), ] %>%
  mutate(TWOWEEK = droplevels(TWOWEEK0))

with(spec.df, table(VACCINE, POSTEST))
```

```
##         POSTEST
## VACCINE    0    1
##       0 1709  488
##       1 1644   94
```

The specimen-based sample has 3935 illness episodes from 3247. 582 of the illness episodes are cases.

Random Specimen-Based Sample

In the random specimen-based sample, we randomly select one eligible SARS-CoV-2 test from each illness episode included in the specimen-based sample instead of choosing the earliest SARS-CoV-2 positive test from a positive episode or earliest SARS-CoV-2 negative test from a negative episode. The random specimen-based sample investigates case status misclassification from SARS-CoV-2 test accuracy. The random specimen-based sample and specimen-based sample will have the same number of participants and illness episodes contributed, but the random specimen-based sample will have as many or fewer cases than the specimen-based sample.

```
# Randomly Choosing One Test Per Illness Episode
# Use Same Participants and Illness Visits from Specimen-Based Sample
# So Choice of Test is Only Source of Randomness
rspec.df0 <- left_join(spec.df[c("USUBJID","EPISODE")], tnd.test.df)
rspec.df <- rspec.df0 %>% group_by(USUBJID, EPISODE) %>%
  slice_sample(n = 1, replace = FALSE) %>%
  mutate(TWOWEEK = droplevels(TWOWEEK0))

with(rspec.df, table(VACCINE, POSTEST))
```

```
##         POSTEST
## VACCINE    0    1
##       0 1767  430
##       1 1657   81
```

The random specimen-based sample has 3935 illness episodes from 3247. 511 of the illness episodes are cases.

Participant-Based Sample without Censoring for COVID-19

Next, we create the participant-based sample without censoring, in which cases are participants with at least one positive episode and contribute their earliest eligible SARS-CoV-2 positive test from their first positive episode and noncases are participants with at least one negative episode (even if they also had a positive episode during the study) and contribute their earliest eligible SARS-CoV-2 negative test from their first negative episode.

```
# Take Earliest Negative Test from Earliest Negative Episode
part.neg.df <- spec.df %>% filter(POSTEST==0) %>%
  group_by(USUBJID) %>% arrange(USUBJID, TESTDT) %>% slice(which.min(TESTDT))

# Take Earliest Positive Test from Earliest Positive Episode
part.pos.df <- spec.df %>% filter(POSTEST==1)

# Put Negative and Positive Episodes Together
# Participants Have Up to 1 Positive and Up to 1 Negative Test
part.woc.df0 <- rbind(part.pos.df, part.neg.df)

part.woc.df <- part.woc.df0 %>%
  mutate(TWOWEEK = droplevels(TWOWEEK0))

with(part.woc.df , table(VACCINE, POSTEST))
```

```
##         POSTEST
## VACCINE    0    1
##       0 1372  488
##       1 1335   94
```

The participant-based sample without censoring has 3289 participants and 582 cases.

Participant-Based Sample with Censoring for COVID-19

Lastly, we create the participant-based sample with censoring, in which cases are participants with at least one positive episode and contribute their earliest eligible SARS-CoV-2 positive test from their first positive episode and noncases are participants with no positive episodes and only negative episodes and contribute their earliest eligible SARS-CoV-2 negative test from their first negative episode.

```
part.wcc.df0  <- spec.df %>% group_by(USUBJID) %>% arrange(USUBJID, TESTDT) %>%
  slice(which.max(POSTEST))

part.wcc.df <- part.wcc.df0 %>%
  mutate(TWOWEEK = droplevels(TWOWEEK0))

with(part.wcc.df , table(VACCINE, POSTEST))
```

```
##         POSTEST
## VACCINE    0    1
##       0 1339  488
##       1 1326   94
```

The participant-based sample with censoring has 3247 participants and 582 cases.

Non-SARS-CoV-2 Illness

One of the core TND assumptions for valid estimation is Noncase Exchangeability, which assumes that vaccinated and unvaccinated individuals in the healthcare-seeking population with the same demographic and clinical characteristics have the same probability of meeting the COVID-19 symptom definition and testing SARS-CoV-2 negative. In the manuscript, we evaluate if any COVID-19 vaccines affect the probability of experiencing non-SARS-CoV-2 illness (meeting the symptom definition and testing negative), which would violate this assumption. In the RCT cohort, we define non-SARS-CoV-2 illness as participants who have a negative episode (meet the symptom definition and have only negative eligible SARS-CoV-2 negative tests). We do not censor for SARS-CoV-2 positive episodes.

```
## Adding Non-SARS-CoV-2 Illness Variables to RCT Cohort (Not TND Sample)

# Take Earliest Negative Episodes per Participant
part.neg.df <- part.neg.df %>% mutate(
  # Non-SARS-CoV-2 Illness
  NEG = 1-POSTEST,
  # Date of Non-SARS-CoV-2 Illness
  NEGADTO= TESTDT
)

rct.df<-left_join(rct.df, part.neg.df[c("USUBJID","NEG","NEGADTO")])
```

```
rct.df <- rct.df %>% rowwise() %>% mutate(
    # Non-SARS-CoV-2 Date is Date of Negative Episode or End of Study
    NEGADT = min(NEGADT0, ENDDT, na.rm=TRUE),
    # Time to Non-SARS-CoV-2 Illness or Censoring
    NEGTT = as.numeric(NEGADT - (DOSE2DT+14) + 1),
    # Non-SARS-CoV-2 Illness Status
    NEG = ifelse(!is.na(NEGADT0) & NEGADT0==NEGADT, 1, 0))

with(rct.df , table(VACCINE, NEG))
```

```
##         NEG
## VACCINE     0     1
##       0 13639  1372
##       1 13654  1335
```

The RCT cohort has 2707 participants with non-SARS-CoV-2 illness.

Statistical Analyses

In this next section, we estimate vaccine efficacy against COVID-19 in the RCT cohort, vaccine effectiveness against COVID-19 using two statistical methods in the four TND samples , and vaccine efficacy against non-SARS-CoV-2 illness in the RCT cohort.

RCT COVID-19 Vaccine Efficacy

```
# Cox PH Model
rct.mod <- coxph(Surv(RCTTT, RCTCASE)~ VACCINE, data = rct.df)
rct.ve<- round(1-summary(rct.mod)$conf.int["VACCINE","exp(coef)"], 3)*100
rct.veCIlow <- round(1-summary(rct.mod)$conf.int["VACCINE","upper .95"], 3)*100
rct.veCIhigh <- round(1-summary(rct.mod)$conf.int["VACCINE","lower .95"],3)*100
```

From the RCT cohort of 3×10^4 participants, we estimate vaccine efficacy, defined as 1 minus the hazard ratio (vaccine vs. placebo), using an unadjusted Cox proportional hazards regression model. RCT vaccine efficacy against COVID-19 is 80.7% (95% CI: 76.4, 84.1).

TND COVID-19 Vaccine Effectiveness Using Semiparametric Logistic Regression

We use the `causalglm` R package developed by Lars van der Laan (https://tlverse.org/causalglm/), which implements semiparametric and nonparametric generalized linear models using targeted maximum likelihood estimation to conduct causal inference on heterogeneous treatment effects. The package relies on `tlverse/tmle3` for targeted maximum likelihood estimation and `tlverse/sl3` and `tlverse/hal9001` for machine-learning. The package is in active development so please contact Lars van der Laan if there are any issues or concerns (vanderlaanlars@yahoo.com). Make sure to load the most up to date version of these packages from Github.

```
#  Install devtools CRAN package
if(!require(devtools)) {
  install.packages(devtools)
}

# Install Github Packages
devtools::install_github("tlverse/causalglm")
devtools::install_github("tlverse/hal9001@master")
devtools::install_github("tlverse/tmle3@general_submodels_devel")
devtools::install_github("tlverse/sl3@Larsvanderlaan-formula_fix")
```

For our semiparametric logistic regression approach, we apply the partially linear first-order smooth highly adaptive lasso to partially linear logistic regression model of vaccination status (vaccine vs. placebo) on case status, adjusted for age, sex assigned at birth, race/ethnicity, region, comorbidities, and two-week intervals and allowing for two-way interactions. The highly adaptive lasso is the default learning method and recommended in most cases, though other machine-learning methods can be chosen.

To run a semiparametric logistic regression, we use the `spglm` function in `causalglm`, which currently requires all variables in the input dataset to be numerics. We use `model.matrix` to convert all character and factor variables into numeric or indicator variables for each TND sample.

```
## Convert Data to Only Contain Numeric/Indicator Variables (spglm Requirement)
# Use model.matrix to Convert Character/Factor Variables for Each TND Sample
part.woc.semi.model.df <- as.data.frame(model.matrix(~VACCINE + POSTEST + AGE + SEX +
                      POC + REGION + COMORB + TWOWEEK, data=part.woc.df))
part.wcc.semi.model.df <- as.data.frame(model.matrix(~VACCINE + POSTEST + AGE + SEX +
                      POC + REGION + COMORB + TWOWEEK, data=part.wcc.df))
spec.semi.model.df <- as.data.frame(model.matrix(~VACCINE + POSTEST + AGE + SEX +
                      POC + REGION + COMORB + TWOWEEK, data=spec.df))
rspec.semi.model.df <- as.data.frame(model.matrix(~VACCINE + POSTEST + AGE + SEX +
                      POC + REGION + COMORB + TWOWEEK, data=rspec.df))

## Run Semiparametric Model For Each TND Sample (Takes 1-2 Minutes per Model)
part.woc.semi.mod <- spglm(
                # ~ 1 for No Effect Modification,
                formula= ~1,
                # Converted Dataset
                data = part.woc.semi.model.df,
                # Vector of Adjustment Covariate Names from Converted Dataset
                W = setdiff(names(part.woc.semi.model.df),
                            c("(Intercept)","VACCINE","POSTEST")),
                # Regression Predictor of Interest
                A = "POSTEST",
                # Regression Outcome
                Y = "VACCINE",
                estimand = "OR",
                # Default is HAL, Other Methods Include: SuperLearner, glm, glmnet, xgboost
                learning_method = "HAL",
                HAL_args_Y0W = list(smoothness_orders = 1,
                                    max_degree = 2,  # Allows 2-Way Interactions
                                    num_knots = c(10, 10)))

part.wcc.semi.mod <- spglm(
                # ~ 1 for No Effect Modification,
```

```
                formula = ~1,
                data = part.wcc.semi.model.df,
                # Vector of Adjustment Covariate Names from Converted Dataset
                W = setdiff(names(part.wcc.semi.model.df),
                            c("(Intercept)","VACCINE","POSTEST")),
                # Regression Predictor of Interest
                A = "POSTEST",
                # Regression Outcome
                Y = "VACCINE",
                estimand = "OR",
                # Default is HAL, Other Methods Include: SuperLearner, glm, glmnet, xgboost
                learning_method = "HAL",
                HAL_args_YOW = list(smoothness_orders = 1,
                                    max_degree = 2,  # Allows 2-Way Interactions
                                    num_knots = c(10, 10)))

spec.semi.mod <- spglm(
                # ~ 1 for No Effect Modification,
                formula= ~1,
                # Converted Dataset
               spec.semi.model.df,
                # Vector of Adjustment Covariate Names from Converted Dataset
                W = setdiff(names(spec.semi.model.df),
                            c("(Intercept)","VACCINE","POSTEST")),
                # Regression Predictor of Interest
                A = "POSTEST",
                # Regression Outcome
                Y = "VACCINE",
                estimand = "OR",
                # Default is HAL, Other Methods Include: SuperLearner, glm, glmnet, xgboost
                learning_method = "HAL",
                HAL_args_YOW = list(smoothness_orders = 1,
                                    max_degree = 2,  # Allows 2-Way Interactions
                                    num_knots = c(10, 10)))

rspec.semi.mod <- spglm(
                # ~ 1 for No Effect Modification,
                formula= ~1,
                # Converted Dataset
                data= rspec.semi.model.df,
                # Vector of Adjustment Covariate Names from Converted Dataset
                W = setdiff(names(rspec.semi.model.df),
                            c("(Intercept)","VACCINE","POSTEST")),
                # Regression Predictor of Interest
                A = "POSTEST",
                # Regression Outcome
                Y = "VACCINE",
                estimand = "OR",
                # Default is HAL, Other Methods Include: SuperLearner, glm, glmnet, xgboost
                learning_method = "HAL",
                HAL_args_YOW = list(smoothness_orders = 1,
                                    max_degree = 2,   # Allows 2-Way Interactions
                                    num_knots = c(10, 10)))
```

```r
# Model Output
print(part.woc.semi.mod)
```

```
## A causalglm fit object obtained from spglm for the estimand OR with formula:
## log OR(W) = -1.62 * (Intercept)
```

```r
# Example Output
summary(part.woc.semi.mod)
```

```
## A causalglm fit object obtained from spglm for the estimand OR with formula:
## log OR(W) = -1.62 * (Intercept)
##
## Coefficient estimates and inference:
##      type       param tmle_est        se     lower     upper   psi_exp
##    <char>      <char>    <num>     <num>     <num>     <num>     <num>
## 1:     OR (Intercept) -1.62489 0.1194677 -1.859042 -1.390737 0.1969334
##    lower_exp upper_exp  Z_score p_value
##        <num>     <num>    <num>   <num>
## 1: 0.1558218 0.2488917 13.60108       0
```

`print` of an `spglm` object reports the object and equation. `summary` of an `spglm` object reports summary statistics for the sample log conditional odds ratio of vaccination by case status, adjusting for covariates. `tmle_est` is the log conditional odds ratio and `psi_exp` is the conditional odds ratio. `lower_exp` and `upper_exp` are the exponentiated lower and upper bounds of the log conditional odds ratio 95% confidence interval.

Assuming the eleven identifying assumptions specified in the manuscript hold, we can interpret the TND sample conditional odds ratio as the causal conditional risk ratio of COVID-19 comparing vaccinated to unvaccinated healthcare-seeking individuals with the same covariates. Then, using 1 minus the causal conditional risk ratio, TND vaccine effectiveness against virologically-confirmed symptomatic COVID-19 using the semiparametric logistic regression is as follows:

- Participant-Based Sample without Censoring for COVID-19: 80.3% (95% CI: 75.1, 84.4)
- Participant-Based Sample with Censoring for COVID-19: 80.6% (95% CI: 75.5, 84.7)
- Specimen-Based Sample without Censoring for COVID-19: 80% (95% CI: 74.8, 84.2)
- Random Specimen-Based Sample without Censoring for COVID-19: 79.9% (95% CI: 74.3, 84.3)

TND COVID-19 Vaccine Effectiveness Using Ordinary Logistic Regression

We also estimate the TND sample odds ratio of vaccination by case status, adjusted for age, sex assigned at birth, race/ethnicity, region, comorbidities, and two-week intervals main effects using an ordinary logistic regression.

```r
part.woc.ord.mod <- glm(VACCINE ~ POSTEST + AGE + SEX + POC + REGION +
                        COMORB + TWOWEEK, data=part.woc.df, family = "binomial")
part.wcc.ord.mod <- glm(VACCINE ~ POSTEST + AGE + SEX + POC + REGION +
                        COMORB + TWOWEEK, data=part.wcc.df, family = "binomial")
spec.ord.mod <- glm(VACCINE ~ POSTEST + AGE + SEX + POC + REGION +
                        COMORB + TWOWEEK, data=spec.df, family = "binomial")
rspec.ord.mod <- glm(VACCINE ~ POSTEST + AGE + SEX + POC + REGION +
                        COMORB + TWOWEEK, data=rspec.df, family = "binomial")
```

TND vaccine effectiveness against virologically-confirmed symptomatic COVID-19 using the ordinary logistic regression is as follows:

- Participant-Based Sample without Censoring for COVID-19: 80.6% (95% CI: 75.5, 84.7)
- Participant-Based Sample with Censoring for COVID-19: 81% (95% CI: 75.9, 85)
- Specimen-Based Sample without Censoring for COVID-19: 80.2% (95% CI: 75, 84.3)
- Random Specimen-Based Sample without Censoring for COVID-19: 80.1% (95% CI: 74.5, 84.5)

RCT Non-SARS-CoV-2 Illness Vaccine Efficacy

From the RCT cohort of 30,000 participants, we estimate vaccine efficacy against non-SARS-CoV-2 illness, defined as 1 minus the hazard ratio (vaccine vs. placebo), using an unadjusted Cox proportional hazards regression model. While we should evaluate vaccine efficacy in every subgroup adjusted for in a typical TND analysis, for simplicity we only estimated vaccine efficacy in the overall cohort and two age subgroups, less than 60 years old and at least 60 years old.

```
# Cox PH Model
rctneg_mod <- coxph(Surv(NEGTT, NEG) ~ VACCINE, data = rct.df)
rctnegy_mod <- coxph(Surv(NEGTT, NEG) ~ VACCINE, data = subset(rct.df, AGE < 60))
rctnego_mod <- coxph(Surv(NEGTT, NEG) ~ VACCINE, data = subset(rct.df, AGE >= 60))
```

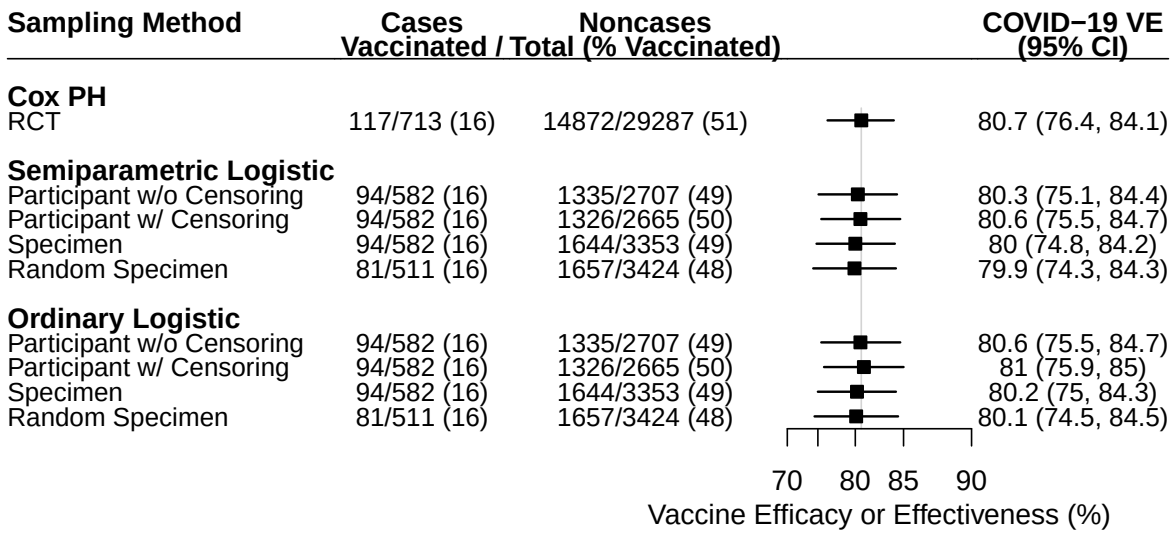
RCT vaccine efficacy against non-SARS-CoV-2 illness is as follows:

- Overall Cohort: 2.7% (95% CI: -5, 9.7, p = 0.484)
- Less than 60 Subgroup: 1.9% (95% CI: -7.6, 10.5, p = 0.686)
- 60 and Over Subgroup: 4.2% (95% CI: -9.2, 15.9, p = 0.524)

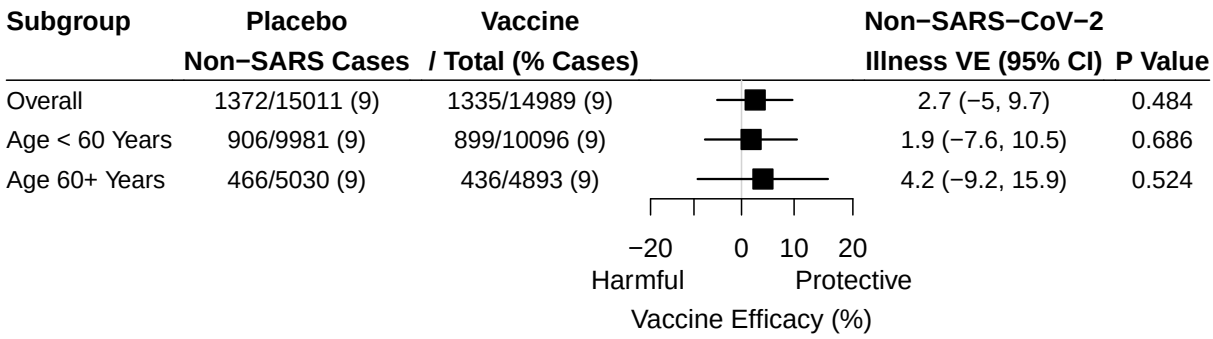
There is no evidence that the vaccine affects non-SARS-CoV-2 illness, which is consistent with our data-generating process.

Summary of Results

We use forest plots to visualize the COVID-19 RCT vaccine efficacy and TND vaccine effectiveness estimates together and the Non-SARS-CoV-2 Illness RCT vaccine efficacy by subgroup.



TND vaccine effectiveness estimates from all sampling approaches and both statistical methods are highly concordant with the RCT vaccine efficacy estimates. The TND estimates' confidence intervals are slightly wider than the RCT estimates' confidence intervals, largely due to the difference in sample size. All confidence intervals overlap.



There is no evidence that the COVID-19 vaccine has an effect on Non-SARS-CoV-2 illness. Thus, the core TND assumption, Noncase Exchangeability, is satisfied and our TND estimates can be interpreted as conditional risk ratios of symptomatic, virologically-confirmed COVID-19 comparing vaccinated and unvaccinated individuals in the healthcare-seeking population with the same characteristics.