Estimation and Hypothesis Testing of Strain-Specific Vaccine Efficacy with Missing Strain Types with Applications to a COVID-19 Vaccine Trial

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Abstract

Statistical methods are developed for analysis of clinical and virus genetics data from phase 3 randomized, placebo-controlled trials of vaccines against novel coronavirus COVID-19. Vaccine efficacy (VE) of a vaccine to prevent COVID-19 caused by one of finitely many genetic strains of SARS-CoV-2 may vary by strain. The problem of assessing differential VE by viral genetics can be formulated under a competing risks model where the endpoint is virologically confirmed COVID-19 and the cause-of-failure is the infecting SARS-CoV-2 genotype. Strain-specific VE is defined as one minus the cause-specific hazard ratio (vaccine/placebo). For the COVID-19 VE trials, the time to COVID-19 is right-censored, and a substantial percentage of failure cases are missing the
infecting virus genotype. We develop estimation and hypothesis testing procedures for strain-specific VE when the failure time is subject to right censoring and the cause-of-failure is subject to missingness, focusing on \( J \geq 2 \) discrete categorical unordered or ordered virus genotypes. The stratified Cox proportional hazards model is used to relate the cause-specific outcomes to explanatory variables. The inverse probability weighted complete-case (IPW) estimator and the augmented inverse probability weighted complete-case (AIPW) estimator are investigated. Hypothesis tests are developed to assess whether the vaccine provides at least a specified level of efficacy against some viral genotypes and whether VE varies across genotypes, adjusting for covariates. The finite-sample properties of the proposed tests are studied through simulations and are shown to have good performances. In preparation for the real data analyses, the developed methods are applied to a pseudo dataset mimicking the Moderna COVE trial.

**Key words**: Augmented inverse probability weighted complete-case estimation; Competing risks model; Cause-specific hazard function; Inverse probability weighted complete-case estimation; COVID-19 vaccine efficacy trial; Stratified Cox proportional hazards model, Missing failure cause.

1 Introduction

Randomized, placebo-controlled vaccine efficacy (VE) trials have demonstrated that several SARS-CoV-2 candidate vaccines prevent acquisition of COVID-19 with VE level above 50% and reaching up to 95% (e.g., Polack et al., 2020; Baden et al., 2020). All of these vaccines use the so-called Wuhan or Washington strain (henceforth WA strain) of SARS-CoV-2 in the vaccine construct. Genetic variability of SARS-CoV-2 viruses has been increasing over time, with several variants emerging that have several genetic mutations compared to the WA strain, generating concern that the level of VE could be lower against certain variants (Lauring and Hodcroft, 2021). For
efficacy results reported through about February 2021, the viruses circulating during
the trial were almost all WA strains or very slight variants (1 or 2 mismatches),
such that the trials did not provide information on VE against variants. For recent
efficacy results for trials in the United Kingdom, Brazil, and South Africa, variants
dominated the circulating strains, such that estimates did assess VE against variants,
and the estimates were lower than for trials in regions where WA strains dominated
(Madhi et al., 2021; Sadoff et al., 2021). To date the published statistical analyses
for understanding how VE may depend on variants has consisted of analyses of VE
against all SARS-CoV-2 strains circulating in a given geographic region, for example
the ENSEMBLE trial of the Ad26.COV2.S vaccine reported an estimate of VE of
66.9% in the U.S. where the WA strain predominated and an estimate of VE of
52.0% in South Africa where the B.1.351 variant strain predominated (Sadoff et al.,
2021).

Many of the COVID-19 VE trials are sequencing the SARS-CoV-2 spike gene for
all COVID-19 primary endpoint cases, where in general the vaccines only include the
spike gene. These data will enable sieve analysis (Gilbert, Ashby, Self, 1998; Edlefsen
et al., 2015; Neafsey et al., 2015; Juraska et al., 2018), which, based on a competing
risks failure time data set-up, assesses whether and how VE depends on genetic
features of the pathogen strain causing the disease endpoint. Rolland and Gilbert
(2021) briefly discussed motivation and applications of sieve analysis in SARS-CoV-2
VE trials. While many statistical methods of sieve analysis have been developed, some
features of the forthcoming data sets for the COVID-19 VE trials require some novel
methods development. First, the methodology needs to allow for missing sequences,
because sequencing technology is only able to measure the spike sequence if the viral
load of the sample used for sequencing is sufficiently high (Xiao et al., 2022). A
wealth of data in natural history studies suggest an expected 20-30% of placebo arm
COVID-19 endpoint cases will have missing sequences, and the rate of missingness
will generally be higher in vaccine arm COVID-19 endpoint cases, given that the
vaccines usually have some impact to suppress viral load. Second, the methodology needs to handle $J$ discrete categorical genotypes with $J > 2$ and allowing the multiple genotypes to be either unordered categorical or ordered categorical (e.g., a Hamming distance that is the number of amino acids in the Spike protein that are mismatched to the WA vaccine strain). Third, it is useful for the methods to provide inferences for whether VE differs across genotypes (with variation termed a “sieve effect”), not only providing separate inferences about VE against each individual genotype. Lastly, the methodology needs to accommodate that the background incidence of COVID-19 can vary over calendar time, given waxing and waning outbreaks. In this work, we focus on addressing these needs through a proportional hazards model, which is reasonable for the COVID-19 VE trials during their primary periods of follow-up, given that these periods last less than 6 months and immune responses induced by the vaccines are fairly stable during these periods. This indicates that the Cox model assumption of time-constant VE against any given genotype is a reasonable assumption, at least approximately.

Among Cox model methods that handle missing causes of failure, Goetghebeur and Ryan (1995) used weighted Cox modeling, and Lu and Tsiatis (2001) used a parametric model for the probability of observing a sequence and used multiple imputation to predict missing genotypes from auxiliary covariates. Adapting the theory of Robins, Rotnitzky, and Zhao (1994), Gao and Tsiatis (2005) considered linear transformation models – with the Cox model a special case – developing inverse probability weighted (IPW) and augmented IPW (AIPW) methods; Hyun et al. (2012) also developed IPW and AIPW methods for the Cox model. These papers focused on two causes of failure, and did not provide techniques for sieve effect tests. Moreover, auxiliary covariates were considered, but for the COVID-19 application auxiliary marks are more valuable. (A ‘mark’ is a random variable only meaningfully defined in failure endpoint cases.) In particular, the key auxiliary mark is the SARS-CoV-2 viral load from the blood sample used for sequencing the virus. In addition, for the applica-
tions it is useful to allow separate baseline hazards for different calendar intervals of enrollment, as one way to handle unpredictable secular trends in placebo COVID-19 arm incidence. While all of the methods could be devised to allow multiple baseline hazards, the available implementations typically do not include this implementation. This current work most closely resembles that of Hyun et al. (2012), where we also develop IPW and AIPW methods, and take on the new features not considered previously of handling $J > 2$ unordered or ordered categorical genotypes, and developing hypothesis testing procedures for multiple new questions of interest including the assessment of sieve effects. The methods are implemented in the R package cmprskPH available at https://github.com/fei-heng/cmprskPH.

The rest of this article is organized as follows. In Section 2 we present the mathematical framework for estimating VE against specific genotypes which are subject to missingness. Section 3 is devoted to demonstrating the development of IPW and AIPW estimation methods. Asymptotic properties for the proposed estimators are established in Section 4 with proofs in the Web Appendix A. In Section 5 the confidence intervals and hypothesis testing procedures for VE are derived. We conduct simulation studies to examine the finite-sample performance of estimators and the tests in Section 6 and we apply our methods to a pseudo dataset mimicking the Moderna COVE trial in Section 7.

2 Stratified cause-specific proportional hazards models and missing causes

Let $\tau$ be the duration of the vaccine trial. Let $T$ be the failure time, $V$ the cause of failure (also termed as discrete mark or type of infecting strain in VE trials), and $Z(t)$ a possibly time-dependent $p$-dimensional covariate. Statistical interest focuses
on the conditional cause-specific hazard rate of cause \( j \) defined by

\[
\lambda_j(t|z(t)) = \lim_{\Delta t \downarrow 0} \frac{1}{\Delta t} P(t \leq T < t + \Delta t \, | \, V = j \land T \geq t, Z(t) = z(t)),
\]

for \( j = 1, \ldots, J \). The function \( \lambda_j(t|z(t)) \) is the instantaneous failure rate from cause \( j \) at time \( t \) in the presence of the other failure types. For VE trials, we specifically consider the covariate \( z(t) = (z_1, z_2(t))^T \), where \( z_1 \) is the treatment group indicator \((1=\text{vaccine}; 0=\text{placebo})\) and \( z_2(t) \) the vector of other covariates. Vaccine efficacy to reduce susceptibility to strain \( j \) at time \( t \) is defined as

\[
VE_j(t|z_2(t)) = 1 - \frac{\lambda_j(t|z_1=1, z_2(t))}{\lambda_j(t|z_1=0, z_2(t))}.
\]

Gilbert (2000) discussed the assumptions required for the strain-specific vaccine efficacy to have a meaningful biological interpretation.

In practice, different key subgroups (e.g., men and women; individuals living in different geographic regions, individuals enrolled during different calendar intervals) typically have different baseline cause-specific hazards of failure. The stratified cause-specific proportional hazard regression model postulates that the conditional cause-specific hazard function for cause \( j \) for an individual in the \( k \)th stratum with the covariate value \( z(t) = (z_1, z_2(t))^T \) equals

\[
\lambda_{kj}(t|z(t)) = \lambda_{0kj}(t) \exp(\beta_j^T z(t)) = \lambda_{0kj}(t) \exp(\alpha_j z_1 + \gamma_j^T z_2(t)),
\]

for \( j = 1, \ldots, J \) and \( k = 1, \ldots, K \), where \( \lambda_{0kj}(\cdot) \) is an unspecified cause-specific baseline hazard function for the \( k \)th stratum and \( K \) is the number of strata. Here \( \beta_j = (\alpha_j, \gamma_j) \) is a \( p \)-vector of regression parameters for the \( j \)th strain. Define \( \beta = (\beta_1, \ldots, \beta_J) \). Model \( \Pi \) allows different baseline functions for different strata. Similar generalizations of the Cox model were studied by Dabrowska (1997). Under model \( \Pi \), the covariate-adjusted strain-specific vaccine efficacy \( VE_j \) is one minus \( \exp(\alpha_j) \).

To ease the notation in the method development, we generally use \( Z(t) = (Z_1, Z_2^T(t))^T \) to represent the covariate process on \([0, \tau]\), denoted by \( Z(\cdot) \). The right-censored failure time data are observations of \((X, \delta, Z(\cdot))\), where \( X = \min\{T, C\} \), \( \delta = I(T \leq C) \),
and $C$ is a censoring random variable. In a competing risks framework, the cause $V$ can only be observed when failure occurs, whereas it is unknown if the failure time $T$ is censored. Then, the completely observed right-censored competing risks data are observations of the random variables $(X, Z(\cdot), V)$ for $\delta = 1$ and $(X, Z(\cdot))$ for $\delta = 0$.

In the presence of missing causes, we introduce a binary indicator, $R$, representing whether all possible data are observed for a subject. $R$ equals to one if either $\delta = 0$ (right-censored) or if $\delta = 1$ and $V$ is observed, and zero otherwise. The auxiliary covariates $A$ may be helpful for predicting missingness and for informing about the distribution of missing causes. $A$ may include useful auxiliary marks because causes can only be missing for failures. In the COVID-19 application presented in Section 7, $A$ is the SARS-CoV-2 viral load measured in COVID-19 endpoint cases, a continuous mark that is possibly associated with the probability of missingness and the strain type $V$.

We assume that the censoring time $C$ is conditionally independent of $(T, V)$ given $Z(\cdot)$ for an individual in the $k$th stratum. We also assume the cause $V$ is missing at random (Rubin, 1976); that is, given $\delta = 1$ and $W = (T, Z(T), A)$ of an individual in the $k$th stratum, the probability that the cause $V$ is missing depends only on the observed $W$, not on the value of $V$; this assumption is expressed as

$$
r_{k}(W) \equiv P(R = 1|\delta = 1, W) = P(R = 1|V = 1, W). \quad (2)
$$

Let $\pi_{k}(Q) = P(R = 1|Q)$ where $Q = (\delta, W)$. Then $\pi_{k}(Q) = \delta r_{k}(W) + (1 - \delta)$. The missing at random assumption (2) also implies that $V$ is independent of $R$ given $Q$:

$$
\rho_{kj}(W) \equiv P(V = j|\delta = 1, W) = P(V = j|R = 1, \delta = 1, W). \quad (3)
$$

For an observed value $w$ of $W$ of an individual in the $k$th stratum, we write $r_{k}(w) = P(R = 1|\delta = 1, W = w)$ and $\rho_{kj}(w) = P(V = j|\delta = 1, W = w)$. The stratum-specific definitions of $r_{k}(w)$ and $\rho_{kj}(w)$ leave the options for the models of the probability of complete-case and cause distribution to be different for different strata.

Let $n_k$ be the number of subjects in the $k$th stratum; the total sample size is $n = \sum_{k=1}^{K} n_k$. Let $\{X_{ki}, Z_{ki}(), \delta_{ki}, R_{ki}, V_{ki}, A_{ki}; i = 1, \ldots, n_k\}$ be iid replicates of $\{X, Z(), \delta, R, V, A\}$ from the $k$th stratum. The observed data are denoted by $\{O_{ki}; i = 1, \ldots, n_k, k = 1, \ldots, K\}$, where $O_{ki} = \{X_{ki}, Z_{ki}(), R_{ki}, R_{ki}V_{ki}, A_{ki}\}$ for $\delta_{ki} = 1$ and $O_{ki} = \{X_{ki}, Z_{ki}(), R_{ki} = 1\}$ for $\delta_{ki} = 0$. We assume that $\{O_{ki}; i = 1, \ldots, n_k, k = 1, \ldots, K\}$ are independent for all subjects. Similarly, we denote $W_{ki} = (T_{ki}, Z_{ki}(T_{ki}), A_{ki})$ and $Q_{ki} = (\delta_{ki}, W_{ki})$.

We consider a parametric model $r_k(W_{ki}, \psi_k)$ for $r_k(W_{ki})$, where $\psi_k$ is an unknown vector of parameters to be further discussed in the next section. Let $\pi_k(Q_{ki}, \psi_k) = \delta_{ki}r_k(W_{ki}, \psi_k) + (1 - \delta_{ki})$. Additional notation is introduced in the following. For $\beta \in \mathbb{R}^p$, $t \geq 0$, let $Y_{ki}(t) = I(X_{ki} \geq t)$,

$$S_k^{(j)}(t, \beta) = n_k^{-1} \sum_{i=1}^{n_k} Y_{ki}(t) \exp\{\beta^T Z_{ki}(t)\} Z_{ki}(t)^{\otimes j},$$

$$\tilde{S}_k^{(j)}(t, \beta, \psi_k) = n_k^{-1} \sum_{i=1}^{n_k} R_{ki}(\pi_k(Q_{ki}, \psi_k))^{-1} Y_{ki}(t) \exp\{\beta^T Z_{ki}(t)\} Z_{ki}(t)^{\otimes j},$$

where for any $z \in \mathbb{R}^p$, $z^{\otimes 0} = 1$, $z^{\otimes 1} = z$ and $z^{\otimes 2} = zz^T$. Define $s_k^{(j)}(t, \beta) = ES_k^{(j)}(t, \beta)$ and $\tilde{s}_k^{(j)}(t, \beta, \psi_k) = E\tilde{S}_k^{(j)}(t, \beta, \psi_k)$. Under the missing at random assumption (2), $s_k^{(j)}(t, \beta) = \tilde{s}_k^{(j)}(t, \beta, \psi_k)$ if the model $r_k(W_{ki}, \psi_k)$ is correctly specified. Let

$$J_k(t, \beta) = \frac{S_k^{(2)}(t, \beta)}{S_k^{(0)}(t, \beta)} - \left(\frac{S_k^{(1)}(t, \beta)}{S_k^{(0)}(t, \beta)}\right)^{\otimes 2},$$

$$\tilde{J}_k(t, \beta, \psi_k) = \frac{\tilde{S}_k^{(2)}(t, \beta, \psi_k)}{\tilde{S}_k^{(0)}(t, \beta, \psi_k)} - \left(\frac{\tilde{S}_k^{(1)}(t, \beta, \psi_k)}{\tilde{S}_k^{(0)}(t, \beta, \psi_k)}\right)^{\otimes 2},$$

$$Z_k(t, \beta) = \frac{S_k^{(1)}(t, \beta)}{S_k^{(0)}(t, \beta)}, \quad \tilde{Z}_k(t, \beta, \psi_k) = \frac{\tilde{S}_k^{(1)}(t, \beta, \psi_k)}{\tilde{S}_k^{(0)}(t, \beta, \psi_k)}.$$

Let $\tilde{z}_k(t, \beta) = s_k^{(1)}(t, \beta)/s_k^{(0)}(t, \beta)$ and $I_k(t, \beta) = s_k^{(2)}(t, \beta)/s_k^{(0)}(t, \beta) - (\tilde{z}_k(t, \beta))^{\otimes 2}$. 
3 Estimation procedures

When there are no missing causes, for each $j$, $\beta_j$ in model (1) can be estimated by maximizing the local log-partial likelihood function

$$l(j, \beta_j) = \sum_{k=1}^{K} \sum_{i=1}^{n_k} \int_0^\tau \left[ \beta_j^T Z_{ki}(t) - \log \left( \sum_{j=1}^{n_k} Y_{kj}(t) e^{\beta_j^T Z_{kj}(t)} \right) \right] N_{kij}(dt),$$

where $N_{kij}(dt) = I(X_{ki} \leq t, \delta_{ki} = 1, V_{ki} = j)$ is the counting process with a jump at the uncensored failure time $X_{ki}$ and the associated cause $V_{ki} = j$. Taking the derivative of $l(j, \beta)$ with respect to $\beta$ gives the score function

$$U(j, \beta_j) = \sum_{k=1}^{K} \sum_{i=1}^{n_k} \int_0^\tau \left( Z_{ki}(t) - \frac{S_k^{(1)}(t, \beta_j)}{S_k^{(0)}(t, \beta_j)} \right) N_{kij}(dt).$$

The maximum partial likelihood estimator is a solution to $U(j, \beta_j) = 0$.

3.1 Inverse probability weighted complete-case estimation

Following Horvitz and Thompson (1952), inverse probability weighting of complete-cases has been commonly used in missing data problems. Let $r_k(W_{ki}, \psi_k)$ be the parametric model for the probability of complete-case $r_k(W_{ki})$ defined in (2), where $\psi_k$ is a $q$-dimensional parameter. For example, one can assume the logistic model with $\text{logit}(r_k(W_{ki}, \psi_k)) = \psi_k^T W_{ki}$ for those with $\delta_{ki} = 1$. By (2), the maximum likelihood estimator $\hat{\psi} = (\hat{\psi}_1, \ldots, \hat{\psi}_K)$ of $\psi = (\psi_1, \ldots, \psi_K)$ is obtained by maximizing the observed data likelihood,

$$\prod_{k,i} \{r_k(W_{ki}, \psi_k)\}^{R_{ki} \delta_{ki}} \{1 - r_k(W_{ki}, \psi_k)\}^{(1-R_{ki})\delta_{ki}}.\tag{6}$$

We propose the following inverse probability weighted (IPW) estimating equation for $\beta$:

$$U_1(j, \beta_j, \hat{\psi}) = \sum_{k=1}^{K} \sum_{i=1}^{n_k} \int_0^\tau \left( Z_{ki}(t) - \tilde{Z}_k(t, \beta_j, \hat{\psi}_k) \right) \frac{R_{ki}}{\pi_k(Q_{ki}, \hat{\psi}_k)} N_{kij}(dt).\tag{7}$$
The IPW estimator of $\beta_j$ solves the above equation and is denoted by $\hat{\beta}_{j,I}$.

Let $\Lambda_{0kj}(t) = \int_0^t \lambda_{0kj}(s) \, ds$ be the cumulative baseline function for each $k$ and $j$. Let $K(\cdot)$ be a kernel function with bandwidth $h$ and $K_h(x) = K(x/h)/h$. The baseline function $\lambda_{0kj}(t)$ can be estimated by $\hat{\lambda}_{0kj}^I(t)$, obtained by smoothing the increments of the following estimator of the cumulative baseline function $\Lambda_{0kj}(t)$:

$$
\hat{\lambda}_{0kj}^I(t) = \int_0^t K_h(t-s) \hat{\Lambda}_{0kj}^I(ds),
$$

where

$$
\hat{\Lambda}_{0kj}^I(t) = \sum_{i=1}^{n_k} \int_0^t \frac{R_{ki}}{\pi_k(Q_{ki}, \hat{\psi}_k)} \frac{N_{kij}(ds)}{n_k \tilde{S}_k^{(0)}(s, \hat{\beta}_{j,I}, \hat{\psi}_k)}.
$$

### 3.2 Augmented inverse probability weighted complete-case estimation

The IPW estimator $\hat{\beta}_{j,I}$ uses only complete cases and is inefficient. To increase estimation efficiency, we propose the augmented inverse probability weighted complete-case (AIPW) estimating function following the idea of Robins et al. (1994). The proposed AIPW estimating equation utilizes available information for individuals with missing causes through a consistent estimator of $\rho_{kj}(W)$, the conditional distribution of the failure cause.

In the case that $\sum_{j=1}^{J-1} \rho_{kj}(W_{ki}) = 1$, we posit parametric models $\rho_{kj}(W_{ki}, \varphi_{kj})$ for $\rho_{kj}(W_{ki})$ for $j = 1, \ldots, J-1$, where $\varphi_{kj}$ are unknown parameters. It is natural to use a logistic multinominal regression model $\text{logit}\{\rho_{kj}(W_{ki}, \varphi_{kj})\} = W_{ki}^T \varphi_{kj}$ for $j = 1, \ldots, J-1$, but other parametric models can also be accommodated. Under the MAR assumption (3), $\rho_{kj}(W_{ki})$ can be estimated using the complete cases with $R_{ki} = 1$ and $\delta_{ki} = 1$. The maximum likelihood estimator $\hat{\varphi}_{kj}$ of $\varphi_{kj}$ can be obtained by maximizing the likelihood based on complete-case data

$$
\prod_{k=1}^{K} \prod_{i=1}^{n_k} \left( \prod_{j=1}^{J-1} \rho_{kj}(W_{ki}, \varphi_{kj}) \right)^{I(V_{ki}=j)R_{ki}\delta_{ki}} \{1 - \prod_{j=1}^{J-1} \rho_{kj}(W_{ki}, \varphi_{kj}) \}^{I(V_{ki}=J)R_{ki}\delta_{ki}}.
$$
Since $\hat{\varphi}_{kj}$ is the maximum likelihood estimator, it follows that for a correctly specified model $\rho_{kj}(W_{ki}, \varphi_{kj})$, $\hat{\varphi}$ consistently estimates $\varphi_{kj}$, the true value of the parametric component model $\rho(W_{ki}, \varphi)$. Denote $\hat{\rho}_{kj}(W_{ki}) = \rho_{kj}(W_{ki}, \hat{\varphi}_{kj})$ for $j = 1, \ldots, J - 1$. Then, $\rho_{kj}(W_{ki})$ can be consistently estimated by $\hat{\rho}_{kj}(W_{ki}) = 1 - \sum_{j=1}^{J-1} \hat{\rho}_{kj}(W_{ki})$. Let $\hat{\rho}(\cdot) = \{\hat{\rho}_{kj}(W_{ki}), k = 1, \ldots, K, j = 1, \ldots, J\}$.

Let $N_{ki}^r(t) = I(X_{ki} \leq t, \delta_{ki} = 1)$, $N_{ki}^w(v) = I(V_{ki} \leq v)$. Following Robins et al. (1994), we obtain the following AIPW estimating equation for $\beta$:

$$U_A(j, \beta_j, \hat{\psi}, \hat{\rho}(\cdot)) = \sum_{k=1}^{K} \sum_{i=1}^{n_k} \int_0^\tau (Z_{ki}(t) - \bar{Z}_k(t, \beta_j)) \left\{ \frac{R_{ki}}{\pi_k(Q_{ki}, \hat{\psi})} N_{ki}^r(dt) + \left(1 - \frac{R_{ki}}{\pi_k(Q_{ki}, \hat{\psi})}\right) \hat{\rho}_{kj}(W_{ki}) N_{ki}^w(ds) \right\} .$$

The AIPW estimator of $\beta_j$ solves the above equation and is denoted by $\hat{\beta}_{j,A}$. We can similarly estimate the baseline hazard function $\lambda_{0kj}(t)$ by a kernel estimator $\hat{\Lambda}_{0kj}^A(t) = \int_0^t K_h(t-s) \hat{\Lambda}_{0kj}^A(ds)$, where

$$\hat{\Lambda}_{0kj}^A(t) = \sum_{i=1}^{n_k} \int_0^t \frac{R_{ki}}{\pi_k(Q_{ki}, \hat{\psi})} \frac{N_{ki}^w(ds)}{n_k S_k^{(0)}(s, \hat{\beta}_{j,A})} + \left(1 - \frac{R_{ki}}{\pi_k(Q_{ki}, \hat{\psi})}\right) \hat{\rho}_{kj}(W_{ki}) N_{ki}^w(ds)$$

is an estimator of the cumulative baseline function $\Lambda_{0kj}(t)$.

## 4 Asymptotic properties of IPW and AIPW estimators

We investigate the asymptotic properties of the IPW estimator $\hat{\beta}_I = (\hat{\beta}_{1,I}^T, \ldots, \hat{\beta}_{J,I}^T)^T$ and the AIPW estimator $\hat{\beta}_A = (\hat{\beta}_{1,A}^T, \ldots, \hat{\beta}_{J,A}^T)^T$ in this section. For the theoretical results, we need regularity conditions (A.1)-(A.5), which can be found in the Appendix.
4.1 Asymptotic results of inverse probability weighted complete-case estimator

Let

\[
S_{ki}^\psi = \frac{\delta_{ki}(R_{ki} - r_k(W_{ki}, \psi_k))}{r_k(W_{ki}, \psi_k)(1 - r_k(W_{ki}, \psi_k))} \frac{\partial r_k(W_{ki}, \psi_k)}{\partial \psi_k},
\]

\[
I_k^\psi = E_k \left\{ \frac{\delta_{ki}}{r_k(W_{ki}, \psi_k)(1 - r_k(W_{ki}, \psi_k))} \left( \frac{\partial r_k(W_{ki}, \psi_k)}{\partial \psi_k} \right)^T \right\}. \tag{9}
\]

Then \(S_{ki}^\psi\) and \(I_k^\psi\) be the score vector and information matrix for \(\hat{\psi}_k\) under (6), with \(\hat{\psi}_k - \psi_{k0} = n_k^{-1} \sum_{i=1}^{n_k} (I_k^\psi)^{-1} S_{ki}^\psi + o_p(n_k^{-1/2})\).

The consistency and asymptotic normality of \(\hat{\beta}_I\) are established in the next two theorems.

**Theorem 4.1** Under Condition A, if the model for \(r_k(W_{ki})\) is correctly specified, then \(\hat{\beta}_{j,I} \overset{P}{\to} \beta_j\) uniformly in \(j = 1, \ldots, J\) as \(n \to \infty\).

**Theorem 4.2** Under Condition A, if the model for \(r_k(W_{ki})\) is correctly specified, then we have

\[
n^{1/2}(\hat{\beta}_I - \beta) \overset{D}{\to} N(0, \Sigma^{-1} \Sigma_I^* \Sigma^{-1}),
\]

as \(n \to \infty\), where \(\Sigma = \text{diag}\{\Sigma_j, j = 1, \ldots, J\}\) with \(\Sigma_j\) given in the condition (A.3), \(\Sigma_I^* = \sum_{k=1}^{K} p_k E(\xi_{ki,t}^*)^2\) with \(\xi_{ki,t} = ((\xi_{ki,1,t})^T, \ldots, (\xi_{kJi,t})^T)^T\),

\[
\xi_{ki,t}^* = \int_0^\tau (Z_{ki}(t) - \bar{z}_k(t, \beta_j)) \frac{R_{ki}}{\pi_k(Q_{ki})} M_{ki,j}(dt) + D_{kj} (I_k^\psi)^{-1} S_{ki}^\psi,
\]

\(D_{kj} = E_k D_{kj}\), and

\[
D_{kj} = n_k^{-1} \sum_{i=1}^{n_k} \int_0^\tau (Z_{ki}(t) - \bar{z}_k(t, \beta_j)) \left( \frac{-R_{ki}}{\pi_k(Q_{ki})^2} \frac{\partial \pi_k(Q_{ki}, \psi_k)}{\partial \psi_k} \right)^T M_{ki,j}(dt).
\]

Here \(D_{kj}\) is a \(p \times q\) matrix.

Note that the derivative of \(U_I(j, \beta_j, \hat{\psi})\) with respect to \(\beta_j\) equals

\[
U'_I(j, \beta_j, \hat{\psi}) = - \sum_{k=1}^{K} \sum_{i=1}^{n_k} \int_0^\tau \frac{R_{ki}}{\pi_k(Q_{ki}, \hat{\psi}_k)} \tilde{J}_{k}(t, \beta_j, \hat{\psi}_k) N_{ki,j}(dt),
\]

\(12\)
where \( \bar{I}(t, \beta_j, \hat{\psi}_k) \) is defined at the end of Section 2. Let \( \hat{\Sigma}_{j,I} = -n^{-1} U'_j(j, \hat{\beta}_{j,I}, \hat{\psi}) \) and \( \hat{\Sigma}_I = \text{diag}\{\hat{\Sigma}_{j,I}, j = 1, \ldots, J\} \).

Let \( \hat{D}_{kj}, \hat{I}_k^\psi, \hat{S}_k^\psi \) be the empirical counterparts of \( D_{kj}, I_k^\psi, S_k^\psi \), respectively, obtained by replacing expectation with sample average, \( \psi_k \) with \( \hat{\psi}_k \), and \( M_{kij}(dt) \) with \( \tilde{M}_{kij}(dt) = N_{kij}(dt) - Y_{ki}(t) \exp(\hat{\beta}_{j,I}^T Z_{ki}(t)) d\hat{N}_{okj}(t) \).

Let \( \hat{\Sigma}_I = n^{-1} K \sum_{k=1}^{K} \sum_{i=1}^{n_k} \left( \hat{\xi}_{ki,I}^* \right)^{\otimes 2}, \hat{\xi}_{ki,I}^* = \left( (\hat{\xi}_{k1i,I})^T, \ldots, (\hat{\xi}_{kji,I})^T \right)^T \) and

\[
\tilde{\xi}_{kji,I}^* = \int_0^T [Z_{ki}(t) - \tilde{Z}_k(t, \hat{\beta}_{j,I}, \hat{\psi}_k)] \frac{R_{ki}}{(\pi_k(Q_{ki}, \hat{\psi}_k))^2} \tilde{M}_{kij}(dt) + \hat{D}_{kj}(\hat{I}_k^\psi)^{-1}\hat{S}_k^\psi.
\]

By the consistency of \( \hat{\beta}_j \) and \( \hat{\psi}_k \), \( \Sigma \) and \( \Sigma_I^* \) can be consistently estimated by \( \hat{\Sigma}_I \) and \( \hat{\Sigma}_I^* \), respectively.

Under Theorem 4.2 we have \( n^{1/2}(\hat{\beta}_{j,I} - \beta_j) \overset{D}{\rightarrow} N(0, \Sigma_{j,I}^{-1} \Sigma_{j,I}^{-1}) \), where \( \Sigma_{j,I} = \sum_{k=1}^{K} p_k E_k(\xi_{kji,I}^*)^{\otimes 2} \) for \( j = 1, \ldots, J \) as \( n \rightarrow \infty \). Let \( \hat{\Sigma}_{j,I} = n^{-1} K \sum_{k=1}^{K} \sum_{i=1}^{n_k} (\hat{\xi}_{kji,I}^*)^{\otimes 2} \).

The asymptotic variance of \( n^{1/2}(\hat{\beta}_{j,I} - \beta_j) \) can be consistently estimated by \( (\hat{\Sigma}_{j,I})^{-1} \hat{\Sigma}_{j,I}^*(\hat{\Sigma}_{j,I})^{-1} \). The IPW estimators \( \hat{\beta}_{j,I}, j = 1, \ldots, J \), are not asymptotically independent.

### 4.2 Asymptotic results of augmented inverse probability weighted complete-case estimator

We introduce the following notation:

\[
\mathcal{A}_{kij} = \int_0^T (Z_{ki}(t) - \tilde{Z}_k(t, \beta_j)) \frac{R_{ki}}{\pi_k(Q_{ki}, \psi_k)} M_{kij}(dt),
\]
\[
\mathcal{B}_{kij} = \int_0^T (Z_{ki}(t) - \tilde{Z}_k(t, \beta_j)) \left( 1 - \frac{R_{ki}}{\pi_k(Q_{ki}, \psi_k)} \right) E\{M_{kij}(dt) | Q_{ki}\},
\]
\[
\mathcal{D}_{kj} = n_k^{-1} \sum_{i=1}^{n_k} \int_0^T (Z_{ki}(t) - \tilde{Z}_k(t, \beta_j)) \otimes \left\{ \frac{-R_{ki}}{(\pi_k(Q_{ki}, \psi_k))^2} \frac{\partial \pi_k(Q_{ki}, \psi_k)}{\partial \psi_k} M_{kij}(dt) \right\},
\]
\[
\mathcal{O}_{kij} = \mathcal{D}_{kj}(I_k^\psi)^{-1} S_k^\psi.
\]
The next theorem shows that the AIPW estimator $\hat{\beta}_{j,A}$ is consistent if either $r_k(w, \psi_k)$ or $g_k(a|t, v, z, \theta_k)$ is correctly specified, a double robustness property.

**Theorem 4.3** Assuming Condition A, $\hat{\beta}_{j,A} \xrightarrow{p} \beta_j$ uniformly in $j = 1, \ldots, J$ as $n \to \infty$. This consistency holds if either $r_k(w, \psi_k)$ or $g_kj(a|t, z, \theta_k)$ is correctly specified.

Following the proofs of Theorem 4.2 and 4.3, it is easy to show that $n^{1/2}(\hat{\beta}_{j,A} - \beta_j)$ is asymptotically normal for $j = 1, \ldots, J$ if either $r_k(w, \psi_k)$ or $g_kj(a|t, z, \theta_k)$ is correctly specified. When both $r_k(w, \psi_k)$ and $g_kj(a|t, z, \theta_k)$ are correctly specified, Theorem 4.4 below shows that $\hat{\beta}_{j,A}$ is more efficient than $\hat{\beta}_j$.

**Theorem 4.4** Assuming Condition A, if both $r_k(w, \psi_k)$ and $g_kj(a|t, z, \theta_k)$ are correctly specified for $j = 1, \ldots, J$ and for $k = 1, \ldots, K$, we have

$$n^{1/2}(\hat{\beta}_{A} - \beta) \xrightarrow{D} N(0, \Sigma^{-1} \Sigma_A^{-1}),$$

as $n \to \infty$, where $\Sigma = \text{diag}\{\Sigma_j; j = 1, \ldots, J\}$ with $\Sigma_j$ given in the condition (A.3), $\Sigma_A^* = \sum_{k=1}^K p_k E(\xi_{ki,A}^*) \otimes 2$ with $\xi_{ki,A}^* = ((\xi_{k1i,A}^*)^T, \ldots, (\xi_{kJi,A}^*)^T)^T$, and

$$\xi_{kji,A}^* = \int_0^r (Z_{ki}(t) - \tilde{z}_k(t, \beta_j)) \left[ \frac{R_{ki}}{\pi_k(Q_{ki})} N_{ki}(dt) + \left(1 - \frac{R_{ki}}{\pi_k(Q_{ki})}\right) E\{M_{kij}(dt)|Q_{ki}\} \right].$$

Note that $M_{kij}(t) = \int_0^r [N_{kij}(ds) - Y_{ki}(s)\lambda_{kji}(s|Z_{ki}(s)) ds]$ and $\lambda_{kij}(t|Z_{ki}(t)) = \lambda_{0kij}(t) \exp(\beta_j^T Z_{ki}(t))$. We have

$$\xi_{kji,A}^* = \int_0^r (Z_{ki}(t) - \tilde{z}_k(t, \beta_j)) \left[ \frac{R_{ki}}{\pi_k(Q_{ki})} N_{ki}(dt) + \left(1 - \frac{R_{ki}}{\pi_k(Q_{ki})}\right) \rho_{kji} W_{ki}(s) N_{ki}^x(dt) 
- Y_{ki}(s) \exp(\beta_j^T Z_{ki}(s)) d\Lambda_{0kij}(s) \right].$$

Let $\tilde{\Sigma}_j = -n^{-1}U'_A(j, \hat{\beta}_{j,A}; \bar{\psi}, \hat{\rho}(\cdot))$ and $\tilde{\Sigma}_A = \text{diag}\{\tilde{\Sigma}_j, j = 1, \ldots, J\}$. Let

$$\tilde{\Sigma}_A^* = n^{-1} \sum_{k=1}^K \sum_{i=1}^{n_k} (\xi_{ki,A}^*) \otimes 2, \bar{\xi}_{ki,A}^* = ((\bar{\xi}_{k1i,A}^*)^T, \ldots, (\bar{\xi}_{kJi,A}^*)^T)^T$$

and

$$\xi_{kji,A}^* = \int_0^r (Z_{ki}(t) - \tilde{z}_k(t, \hat{\beta}_{j,A})) \left[ \frac{R_{ki}}{\pi_k(Q_{ki}, \psi_k)} N_{kij}(dt) + \left(1 - \frac{R_{ki}}{\pi_k(Q_{ki}, \psi_k)}\right) \hat{\rho}_{kji}(W_{ki}) N_{ki}^x(dt) 
- Y_{ki}(s) \exp(\beta_j^T A Z_{ki}(s)) d\hat{\Lambda}_{0kij}(s) \right].$$
By the consistency of $\hat{\beta}_A$, $\hat{\psi}$, and $\hat{\rho}(\cdot)$, $\Sigma$ and $\Sigma^*_A$ can be consistently estimated by $\hat{\Sigma}_A$ and $\tilde{\Sigma}_A^*$, respectively.

Under Theorem 4.4, we have $n^{1/2}(\hat{\beta}_{j,A} - \beta_j) \overset{D}{\rightarrow} N(0, \Sigma_j^{-1} \Sigma_{j,A}^* \Sigma_j^{-1})$ for $j = 1, \ldots, J$ as $n \rightarrow \infty$, where $\Sigma_{j,A}^* = \sum_{k=1}^K p_k E(\xi_{kji,A}^*)^{\otimes 2}$. Let $\hat{\Sigma}_{j,A} = n^{-1} \sum_{k=1}^K \sum_{i=1}^{n_k} (\hat{\xi}_{kji,A}^*)^{\otimes 2}$. The asymptotic variance of $n^{1/2}(\hat{\beta}_{j,A} - \beta_j)$ can be consistently estimated by $(\hat{\Sigma}_{j,A})^{-1} \tilde{\Sigma}_{j,A}^* (\hat{\Sigma}_{j,A})^{-1}$. The AIPW estimators $\hat{\beta}_{j,A}$, $j = 1, \ldots, J$, are not asymptotically independent.

The estimator $\hat{\beta}_{j,A}$ is more efficient than $\hat{\beta}_{j,I}$ in the sense that

$$
\text{Cov}\{n^{1/2}(\hat{\beta}_{j,I} - \beta_j)\} = \text{Cov}\{n^{1/2}(\hat{\beta}_{j,A} - \beta_j)\} + \Sigma_j^{-1} \left( \sum_{k=1}^K (n_k/n) \text{Cov}\{O_{k1} - B_{k1}\} \right) \Sigma_j^{-1} + o_p(1).
$$

Equation (12) shows that the asymptotic covariance $\text{Cov}\{n^{1/2}(\hat{\beta}_{j,A} - \beta_j)\}$ is smaller than $\text{Cov}\{n^{1/2}(\hat{\beta}_{j,I} - \beta_j)\}$.

## 5 Statistical inferences for vaccine efficacy

Under the stratified cause-specific Cox model (1), the strain-specific vaccine efficacy $VE_j = 1 - \exp(\alpha_j)$, where $\alpha_j$ is the first component of the covariate coefficient vector $\beta_j$, representing the coefficient for vaccination status. Confidence intervals and hypothesis testing procedures for $\{VE_j, j = 1, \ldots, J\}$ are constructed on the basis of estimators $\beta_I$ and $\beta_A$ obtained in Section 3. For simplicity, we omit the subscripts $I$ and $A$ and generally use $\hat{\beta} = (\hat{\beta}_1, \ldots, \hat{\beta}_J)^T$ for the estimator of $\beta = (\beta_1, \ldots, \beta_J)^T$, $\Omega$ for the covariance matrix of the limiting distribution of $n^{1/2}(\hat{\beta} - \beta)$, and $\hat{\alpha} = (\hat{\alpha}_1, \ldots, \hat{\alpha}_J)^T$ for the estimator of $\alpha = (\alpha_1, \ldots, \alpha_J)^T$.

### 5.1 Confidence intervals

By the asymptotic results in Section 4, $n^{1/2}(\hat{\alpha} - \alpha) \overset{D}{\rightarrow} N(0, \Omega_\alpha)$, as $n \rightarrow \infty$, where $\Omega_\alpha$ is the asymptotic covariance matrix consists of elements in corresponding positions.
of $\Omega$. Let $\hat{\Omega}_\alpha$ be a consistent estimator of $\Omega_\alpha$ and $\hat{\Omega}_{\alpha,ij}$ be the $(i,j)$th entry of $\hat{\Omega}_\alpha$. A large sample 100$(1-\alpha)$% confidence interval for $\alpha_j$ is given by $\hat{\alpha}_j \pm z_{\alpha/2} \hat{\sigma}_j$, $j = 1, \ldots, J$, where $z_{\alpha/2}$ is the upper $\alpha/2$th percentile of the standard normal distribution and $\hat{\sigma}_j = (\hat{\Omega}_{\alpha,jj}/n)^{1/2}$ is an estimate of $\sigma_j$, the standard error of $\hat{\alpha}_j$.

The strain-specific vaccine efficacy $VE_j = 1 - \exp(\alpha_j)$ can be estimated by $\hat{VE}_j = 1 - \exp(\hat{\alpha}_j)$. By the asymptotic property of $\alpha_j$ and the delta method, we have $n^{1/2}(\hat{VE}_j - VE_j) \xrightarrow{D} \mathcal{N}(0, \sigma_j^2 \exp(2\alpha_j))$ for $j = 1, \ldots, J$. An approximate 100$(1-\alpha)$% confidence interval for $VE_j$ is then given by $\hat{VE}_j \pm z_{\alpha/2} \hat{\sigma}_j \exp(\hat{\alpha}_j)$, $j = 1, \ldots, J$. Using the transformation $\log((1-\hat{VE})/(1-VE)) = \hat{\alpha}_j - \alpha_j$, we can construct an alternative large-sample approximation of the 100$(1-\alpha)$% confidence interval for $VE_j$: $[1 - \exp(\hat{\alpha}_j + z_{\alpha/2} \hat{\sigma}_j), 1 - \exp(\hat{\alpha}_j - z_{\alpha/2} \hat{\sigma}_j)]$, $j = 1, \ldots, J$. Our numerical studies show that the latter one has better coverage probability.

To measure how much greater the level of VE is against a strain $V = j$ virus than against a strain $V = i$ virus, we define

$$VD(i, j) = \frac{1 - VE_i}{1 - VE_j} = \exp(\alpha_i - \alpha_j),$$

which can be estimated by $\hat{VD}(i, j) = \exp(\hat{\alpha}_i - \hat{\alpha}_j)$. A larger $VD(i, j)$ value indicates that the vaccine provides greater protection against a strain type $j$ virus than against a strain type $i$ virus. The asymptotic variance of $\hat{\alpha}_i - \hat{\alpha}_j$ can be estimated by $\hat{Var}(\hat{\alpha}_i - \hat{\alpha}_j) = n^{-1}(\hat{\Omega}_{\alpha,ii} + \hat{\Omega}_{\alpha,jj} - 2\hat{\Omega}_{\alpha,ij})$. A large sample 100$(1-\alpha)$% confidence interval for $VD(i, j)$ using the logarithm transformation is

$$\left[\hat{VD}(i, j) \exp \left( -z_{\alpha/2} \sqrt{\hat{Var}(\hat{\alpha}_i - \hat{\alpha}_j)} \right), \hat{VD}(i, j) \exp \left( z_{\alpha/2} \sqrt{\hat{Var}(\hat{\alpha}_i - \hat{\alpha}_j)} \right) \right].$$

### 5.2 Testing strain-specific vaccine efficacy

We propose test procedures to evaluate various hypotheses concerning strain-specific VE. The tests assess if the vaccine provides at least a certain specified level of efficacy against some strains and whether vaccine efficacy varies across strains. The hypothesis tests concerning $VE_j$ are constructed based on the estimator of $\alpha_j$. 

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First, we consider testing \( VE_j \leq VE_0 \) for \( j = 1, \ldots, J \), where \( VE_0 \) is a fixed constant such as 0.30 or 0. Let \( c_0 = \log(1 - VE_0) \). We develop the tests of the null hypothesis (A) that VE is at most \( VE_0 \) against all strains \( H_{A0} : VE_j \leq VE_0 \) for all \( j = 1, \ldots, J \). This is equivalent to testing

\[
H_{A0} : \alpha_j \geq c_0, \text{ for all } j = 1, \ldots, J
\]

versus one of the following alternative hypotheses

\[
H_{A1} : \alpha_j \leq c_0 \text{ with strict inequality for some } j,
\]

\[
H_{A2} : \alpha_j \neq c_0 \text{ for some } j.
\]

Thus, \( H_{A0} \) implies that VE against any strain is no more than \( VE_0 \), say, 30%. The alternative \( H_{A1} \) indicates that the VE is higher than \( VE_0 \) for at least some of the viral strains, while \( H_{A2} \) states that VE differs from \( VE_0 \) for some of the viral strains.

The following test statistics are proposed for detecting departures from \( H_{A0} \) in the directions of \( H_{A1} \) and \( H_{A2} \), respectively:

\[
U_1 = \inf_{1 \leq j \leq J} \frac{\tilde{\alpha}_j - c_0}{\hat{\sigma}_j}, U_2 = \sum_{j=1}^{J} \left( \frac{\tilde{\alpha}_j - c_0}{\hat{\sigma}_j} \right)^2.
\]

The test statistic \( U_1 \) can be used to detect the departure \( H_{A1} \) from \( H_{A0} \) and \( U_2 \) can be used to detect the general departure \( H_{A2} \) from \( H_{A0} \). Under \( H_{A0} \), the test statistic \( U_1 \) has the asymptotic distribution of \( \inf_{1 \leq j \leq J} Z_j/\sigma_j \) and \( U_2 \) has the asymptotic distribution of \( \sum_{j=1}^{J} Z_i^2/\sigma_j^2 \), where the vector \((Z_1, \ldots, Z_J)\) follows a multivariate normal distribution with mean vector \(0 = (0, \ldots, 0)\) and covariance matrix \( \Omega_\alpha \). Let \((\tilde{Z}_1, \ldots, \tilde{Z}_J) \sim N(0, \tilde{\Omega}_\alpha) \). Let \( U_{1,\alpha}^* \) be the \( \alpha \)th percentile of \( U_1^* = \inf_{1 \leq j \leq J} \tilde{Z}_j/\tilde{\sigma}_j \), and \( U_{2,\alpha}^* \) the upper \( \alpha \)th percentile of \( U_2^* = \sum_{j=1}^{J} \tilde{Z}_j^2/\tilde{\sigma}_j^2 \), respectively. If \( U_1 < U_{1,\alpha}^* \), the test based on the test statistic \( U_1 \) rejects \( H_{A0} \) in favor of the alternative \( H_{A1} \) at the \( \alpha \) level of significance. If \( U_2 > U_{2,\alpha}^* \), the test based on the test statistic \( U_2 \) rejects \( H_{A0} \) in favor of the alternative \( H_{A2} \).

(2) To test VE against each strain \( j, j = 1, \ldots, J \), we test the following hypotheses:

\[
H_{A0j} : VE_j \leq VE_0 \ (\alpha_j \geq c_0)
\]
versus one of the following alternative hypotheses

\[ H_{Aj1} : \ VE_j > VE_0 \ (\alpha_j < c_0), \]
\[ H_{Aj2} : \ VE_j \neq VE_0 \ (\alpha_j \neq c_0). \]

The following test statistics are used for detecting departures from \( H_{Aj0} \) in the directions of \( H_{Aj1} \) and \( H_{Aj2} \), respectively:

\[ U_{1j} = \frac{\hat{\alpha}_j - c_0}{\hat{\sigma}_j}, U_{2j} = \left( \frac{\hat{\alpha}_j - c_0}{\hat{\sigma}_j} \right)^2. \]

The critical values are obtained similar to above but only for one \( j \) at a time. In clinical trials that require the simultaneous test of \( J \) null hypotheses \( \{H_{Aj0}, j = 1, \ldots, J\} \), a common approach is to apply Bonferroni adjustment of the level of significance. While the Bonferroni procedure is simple to implement, it tends to be quite conservative for control of the familywise error rate (FWER), especially when the number of tests is large. Since the test statistics follow multivariate Gaussian distribution asymptotically, we can apply a less conservative step-down Šidák-like procedure here (Holland and Copenhaver, 1987). The corresponding adjusted \( p \)-values are given by

\[ p_{(i)}^{adj} = \max_{i \leq j} \{1 - (1 - p_{(i)})^{J+1-i}\}, \]

where \( \{p_{(i)}; i = 1, \ldots, J\} \) are ordered unadjusted \( p \)-values from smallest to largest.

(3) Next, we develop tests for whether strain-specific VE depends on strain type, so-called “sieve effect” tests. These tests evaluate the null hypothesis (B)

\[ H_{B0} : VE_1 = VE_2 = \cdots = VE_J \]

versus the following alternative hypotheses:

\[ H_{B1} : \ VE_1 \geq \cdots \geq VE_j \geq \cdots \geq VE_J \] with strict inequality for some \( 1 \leq j \leq J \),
\[ H_{B2} : \ VE_i \neq VE_j \] for at least one pair of \( i \) and \( j \), \( 1 \leq i < j \leq J \).

\( H_{B0} \) implies that strain-specific VE does not vary with strain type. The ordered alternative \( H_{B1} \) states that VE decreases with strain type. Under the proportional hazards model (1) the hypotheses (B) can be rewritten as

\[ H_{B0} : \ \alpha_1 = \alpha_2 = \cdots = \alpha_J \]
against the following alternative hypotheses

\[ H_{B1} : \ \alpha_1 \leq \cdots \leq \alpha_j \leq \cdots \leq \alpha_J \text{ with at least one strict inequality}, \]

\[ H_{B2} : \ \alpha_i \neq \alpha_j \text{ for at least one pair of } i \text{ and } j, \quad 1 \leq i < j \leq J. \]

The following test statistic \( T_1 \) is suggested for detecting the monotone departure \( H_{B1} \) from \( H_{B0} \):

\[
T_1 = \inf_{2 \leq j \leq J} \frac{\hat{\alpha}_j - \hat{\alpha}_{j-1}}{\sqrt{\hat{\text{Var}}(\hat{\alpha}_j - \hat{\alpha}_{j-1})}},
\]

where \( \hat{\text{Var}}(\hat{\alpha}_j - \hat{\alpha}_{j-1}) \) is the estimate of \( \text{Var}(\hat{\alpha}_j - \hat{\alpha}_{j-1}) = \text{Var}(\hat{\alpha}_j) - 2\text{Cov}(\hat{\alpha}_{j-1}, \hat{\alpha}_j) + \text{Var}(\hat{\alpha}_{j-1}) \), which can be obtained from \( \hat{\Omega}_\alpha \). Under \( H_{B0} \), asymptotically, we can approximate \( T_1 \) by \( T_1^* = \inf_{2 \leq j \leq J} (\hat{Z}_j - \hat{Z}_{j-1})/\sqrt{\hat{\text{Var}}(\hat{\alpha}_j - \hat{\alpha}_{j-1})} \). The \( H_{B0} \) is rejected in favor of \( H_{B1} \) at significance level \( \alpha \) if \( T_1 > T_{1,\alpha}^* \), where \( T_{1,\alpha}^* \) is the upper \( \alpha \)th percentile of \( T_1^* \). To detect general alternative \( H_{B2} \) from \( H_{B0} \), we consider the test statistic

\[
T_2 = \sum_{j=2}^{J} \frac{(\hat{\alpha}_j - \hat{\alpha}_{j-1})^2}{\hat{\text{Var}}(\hat{\alpha}_j - \hat{\alpha}_{j-1})}.
\]

The asymptotic distribution of test statistic \( T_2 \) under \( H_{B0} \) can be approximated by the distribution of \( T_2^* = \sum_{j=2}^{J} (\hat{Z}_j - \hat{Z}_{j-1})^2/\hat{\text{Var}}(\hat{\alpha}_j - \hat{\alpha}_{j-1}) \). The \( H_{B0} \) is rejected in favor of \( H_{B2} \) if \( T_2 > T_{2,\alpha}^* \), where \( T_{2,\alpha}^* \) is the upper \( \alpha \)th percentile of \( T_2^* \).

6 Simulation study

We conduct a simple simulation study to examine the performance of the proposed methods. We consider a \( p = 2 \) dimensional covariate \( Z = (Z_1, Z_2) \), where \( Z_1 \) is a Bernoulli random variable with probability of success 0.5 that represents the treatment group indicator, and \( Z_2 \) is a uniformly distributed random variable on (0, 1).

We consider the following cause-specific proportional hazards model for \( J = 2 \) causes and \( K = 3 \) strata:

\[
\lambda_{kj}(t|z) = t^{\theta_{kj}} \exp(\alpha_j z_1 + \gamma_j z_2), \quad j = 1, 2, \quad k = 1, 2, 3, \quad (13)
\]
where $\theta_{kj}$, $\alpha_j$ and $\gamma_j$ are the parameters to be specified. All failure times greater than $\tau = 1$ are right-censored at $\tau$. In addition, random censoring times are generated from an exponential distribution, independent of $(T,V)$, with parameter adjusted so approximately 40% of the observations are censored. The sizes and powers of the tests at the nominal 0.05 level are estimated from 1000 independent samples.

We consider a single auxiliary covariate $A$ that follows a Bernoulli distribution with success probability of 0.5. For the cause $V = j$, we also generate a single auxiliary mark variable $A$ that follows a uniform distribution on $(2a(j - 1), 1 + 0.5a_j)$. We examine the performance of the estimators under three different levels of association between $A$ and the failure cause $V$, by considering the settings $a = 0, 0.2, 0.5$, which result in approximate Kendall’s tau values of 0, 0.3, and 0.6, respectively. These three auxiliary association level settings are denoted by (Aux0), (Aux1), and (Aux2), respectively. Note that $A$ is independent of $V$ for the setting (Aux0), and the association between $A$ and $V$ increases from (Aux1) to (Aux2).

The cause $V$ is missing at random (MAR). $r_k(W)$, the conditional probability that the cause is not missing when $\delta = 1$ for $k$-th stratum, follows a logistic regression model \[
\text{logit}\{r_k(W, \psi)\} = \psi_1 + \psi_2 Z_1 + \psi_3 A.
\]

With $\psi = (1.5, -1, -0.5)$, we have about 45% missingness for $Z_1 = 1$ and about 20% missingness for $Z_1 = 0$. Since only two causes are considered in this simulation study, we posit a logistic regression model \[
\text{logit}\{\rho_k(W, \varphi)\} = \varphi_1 + \varphi_2 Z_1 + \varphi_3 A
\]
for $\rho_k(W)$, the probability $P(V = 2|\delta = 1, W)$ in the $k$-th stratum. The parameter $\rho_k(W)$ is estimated by $1 - \rho_k(W, \hat{\varphi})$.

We conducted simulations with sample size $n = 1200$ and with different sets of values for $\theta_{kj}$, $\alpha_j$ and $\varphi_j$, $j = 1, 2$, $k = 1, 2, 3$. We choose $(\theta_{11}, \theta_{12}) = (0.2, 0.2), (\theta_{21}, \theta_{22}) = (0.5, 0.5), (\theta_{31}, \theta_{32}) = (1, 1)$, and $(\gamma_1, \gamma_2) = (1, 1)$. The following parameter settings of $\alpha_j = \log(1 - VE_j)$ are considered for testing $H_{A0}$, $H_{Aj0}$, and $H_{B0}$ against the alternative hypotheses defined in Section 5.2: $j = 1, 2$, where $c_0 = \log(1 - VE_0) = \log(1 - 0.3) = -0.3567$:

(1) For testing $H_{A0}$ and $H_{Aj0}$, $j = 1, 2$, $M_1$: $(\alpha_1, \alpha_2) = (\log(1 - 0.3), \log(1 - 0.3), \log(1 - 0.3))$;
0.3)), $M_2$: $(\alpha_1, \alpha_2) = (\log(1 - 0.5), \log(1 - 0.3))$, and $M_3$: $(\alpha_1, \alpha_2) = (\log(1 - 0.6), \log(1 - 0.3))$;

(2) For testing $H_{B0}$, $N_1$: $(\alpha_1, \alpha_2) = (\log(1 - 0.5), \log(1 - 0.5))$, $N_2$: $(\alpha_1, \alpha_2) = (\log(1 - 0.7), \log(1 - 0.5))$, and $N_3$: $(\alpha_1, \alpha_2) = (\log(1 - 0.9), \log(1 - 0.5))$.

The estimation procedures are examined under the setting $M_3$ of model (13). IPW and AIPW estimators are compared with the complete-case (CC) estimator, which is obtained by solving (5) based on the complete data only. Tables 1 and 2 show biases, the sample standard errors (SSE), the mean of the estimated standard errors (ESE), and 95% empirical coverage probabilities (CP) of the estimators of $\alpha_1$, $\alpha_2$, $VE_1$, $VE_2$, and $VD(2, 1)$ under the setting $M_3$ of model (13) for $n = 1200$ based on 1000 simulations. Both IPW and AIPW estimators have reasonably small bias when the model for $r_k(W)$ is correctly specified. The standard error estimators are fairly accurate, and the 95% confidence intervals have reasonable coverage probabilities. The AIPW estimators are more efficient than IPW estimators, achieving more efficiency gain as the association between auxiliary $A$ and cause $V$ strengthens.

The observed sizes and powers of the tests are examined under the settings $M_1$ to $M_3$ for testing $H_{A0}$ and $H_{A_j0}$, $j = 1, 2$, and $N_1$ to $N_3$ for testing $H_{B0}$, where $M_1$ and $N_1$ are the null hypotheses under $H_{A0}$ and $H_{B0}$, respectively. Tables 3, 4, and 5 report empirical sizes and powers of the test statistics $\{U_1, U_2\}$ for testing $H_{A0}$, the test statistics $\{U_{1j}, U_{2j}\}$ for testing $H_{A_j0}$, $j = 1, 2$, and the test statistics $\{T_1, T_2\}$ for testing $H_{B0}$ under model (13) for $n = 1200$ at nominal level 0.05 based on 1000 simulations. The empirical levels from all tests are closer to the nominal level 0.05 for both IPW and AIPW methods. The powers increase as the extend of departure from the corresponding null hypothesis increases. When the correlation between auxiliary $A$ and cause $V$ becomes stronger, powers using AIPW method increase and are slightly higher than those using IPW methods.
7 An application to a pseudo dataset for the Moderna COVE vaccine efficacy trial

We apply the proposed methods to a pseudo dataset designed to approximate the Moderna COVE vaccine efficacy trial of the mRNA-1273 vaccine (Baden et al., 2020). The primary endpoint is virologically confirmed COVID-19 disease (e.g., Krause et al., 2020, Lancet; Mehrotra et al., 2020, Ann Int Med). The data set approximately fits the Moderna COVE trial design, in terms of numbers of enrolled study participants, numbers of COVID-19 endpoints in the two treatment groups, and through analysis of 1122 randomly sampled real SARS-CoV-2 Spike protein sequences downloaded from GISAID to determine the strain type (i.e. cause) \( V \) with a realistic distribution of interest.

The COVE trial randomized adults at risk for COVID-19 to vaccine or placebo in one-to-one allocation (administered at Day 1 and Day 29), and was designed to follow participants for occurrence of the COVID-19 primary endpoint for 2 years. Participants were enrolled and followed starting on July 27, 2020, and in late December of 2020 the U.S. FDA granted Emergency Use Authorization to the vaccine based on its demonstrated high vaccine efficacy. Shortly after that, a process began to unblind study participants and to offer the vaccine to placebo recipients. Our analysis restricts to the primary period of follow-up (pre-unblinding) and to the participants who tested negative for SARS-CoV-2 at enrollment and who received both vaccinations without specified protocol violations (the primary analysis cohort). Following the protocol-specified primary analysis COVID-19 endpoints are counted starting 14 days post dose 2; we use as time origin 13 days post dose 2.

The data set includes 13,271 participants in the vaccine group with 72 COVID endpoint cases and 13,299 participants in the placebo group with 713 COVID endpoint cases. To mimick the sequences expected from placebo arm COVID-19 endpoint cases in the COVE trial, the sample of 1122 Spike protein sequences from GISAID was
drawn from sequences with deposition date between September 8, 2020 and February 1, 2021 (the approximate period of primary endpoint occurrence during blinded follow-up in the COVE trial) and with location the city of a COVE trial study site. Based on the 1122 sampled GISAID sequences, the vast majority of amino acid positions (of 1273 positions in Spike) have more than 99% of sequences matching the WA strain residue; for these positions there is not enough variability to support sieve analysis. However, for 7 amino acid positions, between 35 and 50 sequences (about 3 to 5%) have a WA-strain mismatched residue; moreover one variant of concern (B.1.429, the “California strain”) has prevalence 3.2%. Based on these data, for placebo arm endpoint cases we generate $V$ from a Bernoulli random variable with success probability 0.04, which represents evaluation in sieve analysis of one of the 7 amino acid positions ($V = 0$ is the WA strain residue, $V = 1$ is the non-WA strain residue), or of the B.1.429 variant ($V = 0$ is the WA strain, $V = 1$ is the B.1.429 variant). To create a sieve effect where VE is less against the $V = 1$ genotype, for vaccine recipients we draw $V$ from a Bernoulli distribution with success probability 0.10.

$V$ was measured from 25 (34.7%) of the 72 vaccine recipient cases and from 382 (53.6%) of the 713 placebo recipient cases. Because the SARS-CoV-2 viral load ($VL$) is correlated with the probability of missingness and the strain type $V$, we consider it as an auxiliary variable in the analysis. A special problem that needs to be addressed is that samples with low viral load may have the probability of missingness very close to 1. This “positivity problem” can make methods that use inverse probability weighting perform unstably. To allow our IPW and AIPW methods to work more robustly, we classify the COVID-19 endpoint participants with low viral load as a minor type of failure causes while the study endpoint of interest is still COVID-19. Specifically, $V$ is redefined as the cause of failure with three types: 1 = vaccine-matched genotype AND viral load above minimum threshold; 2 = vaccine-mismatched genotype AND viral load above minimum threshold; and 3 = viral load below minimum threshold. Here, the minimum threshold is chosen large enough such that based on an empirical
analysis COVID-19 endpoint cases with \( VL \) at the minimum threshold have at least 0.05–0.10 probability that the sequence genotype is observed. We use the minimum threshold \( h_0 = 1 \) for illustration.

Since the cause \( V = 3 \) can be determined based on the observed viral load \(< h_0 \) (an auxiliary variable), the probability of it being not missing is one conditional on the observed viral load. The missing at random (MAR) assumption still holds:

\[
P(R = 1|\delta = 1, T, Z, VL, h_0, V) \\
= P(R = 1|\delta = 1, T, Z, VL, h_0) \\
= I(VL < h_0) + P(R = 1|\delta = 1, T, Z, VL, VL \geq h_0)I(VL \geq h_0).
\]

The data analysis uses \( K = 3 \) baseline strata defined by geography and calendar time. Let \( T \) be the time from 13 days post dose 2 until the COVID-19 endpoint. We consider the following stratified cause-specific proportional hazards model:

\[
\lambda_{kj}(t|z) = \lambda_{k0}(t) \exp(\alpha_j Trt + \gamma_{1j} Highrisk + \gamma_{2j} Age_{65} + \gamma_{3j} Minority + \gamma_{4j} Sex),
\]

for \( j = 1, 2, 3 \) and \( k = 1, 2, 3 \), where \( Trt \) is the vaccine group indicator, \( Highrisk \) is the baseline covariate high risk/at-risk pre-existing condition (1=yes, 0=no), \( Age_{65} \) is the age group at enrollment (1=“65+”, 0=“18-64”), \( Minority \) is the baseline co-variate underrepresented minority status (1=minority, 0=non-minority), and \( Sex \) is sex assigned at birth (1=female, 0=male).

Let \( Z = (Trt, Minority, Highrisk, Sex, Age_{65}) \). We fit a logistic regression model with predictors \((1, Trt, VL)\) to estimate the conditional probability \( P(R = 1|\delta = 1, T, Z, VL, VL \geq h_0) \) for each stratum. Note that \( P(V = 3|\delta = 1, T, Z, VL < h_0) = 1 \) and \( P(V = 2|\delta = 1, T, Z, VL < h_0) = P(V = 1|\delta = 1, T, Z, VL < h_0) = 0 \). Therefore, to implement the AIPW method, we only need to estimate \( P(V = 2|\delta = 1, T, Z, VL, VL \geq h_0) \). It is modeled using logistic regression with predictors \((1, T, Trt, VL)\). Then, the estimates of \( P(V = 1|\delta = 1, T, Z, VL, VL \geq h_0) \) can be obtained through the relationship \( P(V = 1|\delta = 1, T, Z, VL, VL \geq h_0) = 1 - P(V = 2|\delta = 1, T, Z, VL, VL \geq h_0) \).
Tables 6-9 report the results for the estimation of covariate effects, the estimation of strain-specific vaccine efficacies, and the hypothesis testing for vaccine efficacies. The analysis show that the vaccine is highly protective against vaccine-matched genotype ($V=1$) with point estimates of VE beyond 90%, but is not effective in protecting against infection when circulating strains are not well matched the vaccine strain. The vaccine efficacy against vaccine-matched genotype is statistically significantly greater than the null level 30% ($p$-value < 0.001) and greater than the VE against vaccine-mismatched genotype ($p$-value < 0.001). The IPW and AIPW methods provide similar results while AIPW estimates are more efficient in terms of estimated standard errors.

To better illustrate our approach for $J > 2$, we perform an additional analysis of this pseudo dataset using another mark variable, the Hamming distance to the vaccine-insert in the Spike protein. The Hamming distance is a count variable, which is the number of differing amino acids between the vaccine insert and the circulating Spike sequence. Some of its values appear less infrequently in the data which may cause an identifiability problem. Thus, we group Hamming distances into four classes: 0; {1, 2, 3, 4}; {5, 6, 7, 8}; and greater than 8. Further considering the low viral load group, we define failure causes $V^*$ as a categorical variable with five levels: 1 = Hamming distance = 0 AND $VL \geq h_0$; 2 = Hamming distance $\in \{1, 2, 3, 4\}$ AND $VL \geq h_0$; 3 = Hamming distance $\in \{5, 6, 7, 8\}$ AND $VL \geq h_0$; 4 = Hamming distance $\geq 9$ AND $VL \geq h_0$; 5 = $VL < h_0$. Results of the analysis using hamming distance are summarized in Tables 10-13. The vaccine efficacy is significantly greater than the null level 30% for hamming distances less than 9. We also confirm a trend that the vaccine provides better protection against circulating viruses with smaller hamming distances.
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Appendix

Let $F_t = \sigma\{I(X_{ki} \leq s, \delta_{ki} = 1), I(X_{ki} \leq s, \delta_{ki} = 0), V_{ki} I(X_{ki} \leq s, \delta_{ki} = 1), Z_{ki}(s); 0 \leq s \leq t, i = 1, \ldots, n_k, k = 1, \ldots, K\}$ be the (right-continuous) filtration generated by the full data processes $\{N_{kij}(s), Y_{ki}(s), Z_{ki}(s); 0 \leq s \leq t, j = 1, \ldots, J, i = 1, \ldots, n_k, k = 1, \ldots, K\}$. Assume $E(N_{kij}(dt)|F_{t-}) = E(N_{kij}(dt)|Y_{ki}(t), Z_{ki}(t))$, that is, the cause-specific instantaneous failure rate at time $t$ given the observed information up to time $t$ only depends on the failure status and the current covariate value. Under model (1), the cause-specific intensity of $N_{kij}(t)$ with respect to $F_t$ equals $Y_{ki}(t)\lambda_{kj}(t|Z_{ki}(t))$. Let $M_{kij}(t) = \int_0^t [N_{kij}(ds) - Y_{ki}(s)\lambda_{kj}(s|Z_{ki}(s)) ds]$. By Aalen and Johansen (1978), for $j \neq j'$, $M_{kij}(\cdot)$ and $M_{kij'}(\cdot)$ are orthogonal square integrable martingales with respect to $F_t$ for $j, j' = 1, \ldots, J$.

Let $F^*_t = F_t \cup \{R_{ki}, \delta_{ki} A_{ki}; i = 1, \ldots, n_k, k = 1, \ldots, K\}$ be the right continuous filtration obtained by adding $R_{ki}$ and $\delta_{ki} A_{ki}$ to $F_t$. Let $Y_{ki}(t)\lambda^*_{kij}(t)$ be the intensity of $N_{kij}(t)$ with respect to $F^*_t$ Then $E(N_{kij}(dt)|F^*_{t-}) = Y_{ki}(t)\lambda^*_{kij}(t) dt$. Assume that $\lambda^*_{kij}(t)$ is continuous in $t$. Let $M^*_{kij}(t) = N_{kij}(t) - \int_0^t Y_{ki}(s)\lambda^*_{kij}(s) ds$. By Aalen & Johansen (1978), the processes $M^*_{kij}(t)$ and $M^*_{kij'}(\cdot), 0 \leq t \leq \tau$ are orthogonal square integrable martingales for $j \neq j'$.

The following regularity conditions are assumed throughout the rest of the paper. Most of the notation can be found at the end of Section 2.

Condition A

(A.1) $\beta_j$ has componentwise continuous second derivatives on $[0, 1]$. For each $k = \ldots$
1, ..., K, the second partial derivative of \( \lambda_{0k}(t, v) \) with respect to \( v \) exists and is continuous on \([0, \tau] \times [0, 1]\). The covariate process \( Z_{ki}(t) \) has paths that are left continuous and of bounded variation, and satisfies the moment condition 

\[
E[\|Z_{ki}(t)\|^4 \exp(2M\|Z_{ki}(t)\|)] < \infty,
\]

where \( M \) is a constant such that \((v, \beta_j) \in [0, 1] \times (-M, M)^p\) for all \( v \) and \( \|A\| = \max_{k,l} |a_{kl}| \) for a matrix \( A = (a_{kl}) \).

(A.2) Each component of \( s_k^{(j)}(t, \theta) \) is continuous on \([0, \tau] \times [-M, M]^p \), \( \tilde{s}_k^{(j)}(t, \theta, \psi_k) \) is continuous on \([0, \tau] \times [-M, M]^p \times [-L, L]^q \) for some \( M, L > 0 \) and \( j = 0, 1, 2 \).

\[
\sup_{t \in [0, \tau], \theta \in [-M, M]^p} \|S_k^{(j)}(t, \theta) - s_k^{(j)}(t, \theta)\| = O_p(n^{-1/2}), \text{ and } \sup_{t \in [0, \tau], \theta \in [-M, M]^p, \psi_k \in [-L, L]^q} \|\tilde{S}_k^{(j)}(t, \theta, \psi_k) - \tilde{s}_k^{(j)}(t, \theta, \psi_k)\| = O_p(n^{-1/2}).
\]

(A.3) The limit \( p_k = \lim_{n \to \infty} n_k/n \) exists and \( 0 < p_k < 1 \). \( s_k^{(0)}(t, \theta) > 0 \) on \([0, \tau] \times [-M, M]^p \) and the matrix \( \Sigma_j = \sum_{k=1}^{K} p_k \Sigma_{kj} \) is positive definite, where \( \Sigma_{kj} = \sum_{k=1}^{K} \int_0^{\tau} I_k(t, \beta_j) \lambda_{0kj}(t) s_k^{(0)}(t, \beta_j) \, dt \).

(A.4) The kernel function \( K(\cdot) \) is symmetric with support \([-1, 1]\) and has bounded variation. The bandwidth satisfies \( nh^2 \to \infty \) and \( nh^5 = O(1) \) as \( n \to \infty \).

(A.5) There is a \( \varepsilon > 0 \) such that \( r_k(W_{ki}) \geq \varepsilon \) for all \( k, i \) with \( \delta_{ki} = 1 \).

Discussion of some of these conditions can be found in Sun et al. (2009).

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Table 1: Biases, sample standard errors (SSE), mean of the estimated standard errors (ESE), and 95% empirical coverage probabilities (CP) of the estimators of \( \alpha_1 \) and \( \alpha_2 \) under the setting \( M_3 \) of model (13) for \( n = 1200 \) based on 1000 simulations.

| Method                        | \( \alpha_1 \) |                  | \( \alpha_2 \) |                  |
|-------------------------------|----------------|-----------------|----------------|-----------------|
|                               | bias          | SSE             | ESE            | CP              | bias          | SSE             | ESE            | CP              |
| Auxiliary association level setting (Aux0): Kendall’s tau = 0 |              |                 |                |                 |              |                 |                |                 |
| CC                            | -0.2609       | 0.1641          | 0.1599         | 0.639           | -0.2621       | 0.1341          | 0.1326         | 0.501           |
| IPW                           | -0.0099       | 0.1563          | 0.1507         | 0.941           | -0.0130       | 0.1218          | 0.1218         | 0.949           |
| AIPW                          | -0.0102       | 0.1536          | 0.1473         | 0.938           | -0.0120       | 0.1157          | 0.1172         | 0.959           |
| Auxiliary association level setting (Aux1): Kendall’s tau = 0.3 |              |                 |                |                 |              |                 |                |                 |
| CC                            | -0.2631       | 0.1655          | 0.1608         | 0.635           | -0.2922       | 0.1371          | 0.1363         | 0.421           |
| IPW                           | -0.0092       | 0.1560          | 0.1516         | 0.946           | -0.0130       | 0.1231          | 0.1235         | 0.952           |
| AIPW                          | -0.0099       | 0.1496          | 0.1455         | 0.945           | -0.0114       | 0.1150          | 0.1164         | 0.960           |
| Auxiliary association level setting (Aux2): Kendall’s tau = 0.6 |              |                 |                |                 |              |                 |                |                 |
| CC                            | -0.2668       | 0.1666          | 0.1620         | 0.621           | -0.3411       | 0.1429          | 0.1428         | 0.324           |
| IPW                           | -0.0088       | 0.1565          | 0.1526         | 0.945           | -0.0137       | 0.1249          | 0.1264         | 0.955           |
| AIPW                          | -0.0084       | 0.1377          | 0.1343         | 0.947           | -0.0111       | 0.1101          | 0.1109         | 0.955           |
Table 2: Biases, sample standard errors (SSE), mean of the estimated standard errors (ESE), and 95% empirical coverage probabilities (CP) of the estimators of $VE_1$, $VE_2$, and $VD(2, 1)$ under the setting $M_3$ of model (13) based on 1000 simulations.

|                | IPW                      | AIPW                     |
|----------------|--------------------------|--------------------------|
|                | bias  | SSE   | ESE   | CP   | bias  | SSE   | ESE   | CP   |
| **Auxiliary association level setting (Aux0): Kendall’s tau = 0** |       |       |       |      |       |       |       |      |
| $VE_1$         | -0.0009 | 0.0628 | 0.0601 | 0.941 | -0.0006 | 0.0614 | 0.0587 | 0.938 |
| $VE_2$         | 0.0039  | 0.0848 | 0.0847 | 0.949 | 0.0037  | 0.0806 | 0.0815 | 0.959 |
| $VD(2, 1)$     | 0.0336  | 0.3785 | 0.3694 | 0.943 | 0.0362  | 0.3814 | 0.3708 | 0.943 |
| **Auxiliary association level setting (Aux1): Kendall’s tau = 0.3** |       |       |       |      |       |       |       |      |
| $VE_1$         | -0.0012 | 0.0629 | 0.0605 | 0.946 | -0.0005 | 0.0599 | 0.0580 | 0.945 |
| $VE_2$         | 0.0038  | 0.0859 | 0.0858 | 0.952 | 0.0033  | 0.0802 | 0.0810 | 0.960 |
| $VD(2, 1)$     | 0.0322  | 0.3772 | 0.3734 | 0.953 | 0.0345  | 0.3693 | 0.3644 | 0.947 |
| **Auxiliary association level setting (Aux2): Kendall’s tau = 0.6** |       |       |       |      |       |       |       |      |
| $VE_1$         | -0.0014 | 0.0630 | 0.0610 | 0.945 | -0.0004 | 0.0549 | 0.0536 | 0.947 |
| $VE_2$         | 0.0041  | 0.0872 | 0.0878 | 0.955 | 0.0035  | 0.0768 | 0.0771 | 0.955 |
| $VD(2, 1)$     | 0.0309  | 0.3806 | 0.3795 | 0.953 | 0.0249  | 0.3282 | 0.3243 | 0.946 |
Table 3: Empirical sizes and powers of the test statistics $U_1$ and $U_2$ for testing $H_{A0}$ under model (13) for $n = 1200$ at nominal level 0.05 based on 1000 simulations.

| Model | Test | IPW | AIPW |
|-------|------|-----|------|
|       |      | $U_1$ | $U_2$ | $U_1$ | $U_2$ |
|       |      | 0.053 | 0.059 | 0.055 | 0.049 |
|       |      | 0.718 | 0.584 | 0.726 | 0.600 |
|       |      | 0.973 | 0.943 | 0.980 | 0.954 |
| (Aux0): Kendall’s tau = 0 |
| $M_1$ | Size | 0.051 | 0.059 | 0.055 | 0.052 |
| $M_2$ | Power| 0.706 | 0.576 | 0.733 | 0.606 |
| $M_3$ |      | 0.972 | 0.942 | 0.981 | 0.958 |
| (Aux1): Kendall’s tau = 0.3 |
| $M_1$ | Size | 0.055 | 0.058 | 0.049 | 0.044 |
| $M_2$ | Power| 0.694 | 0.562 | 0.770 | 0.672 |
| $M_3$ |      | 0.971 | 0.927 | 0.994 | 0.979 |
| (Aux2): Kendall’s tau = 0.6 |

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Table 4: Empirical sizes and powers of the test statistics $U_{1j}$ and $U_{2j}$ for testing $H_{A_{j0}}, j = 1, 2$, under model (13) for $n = 1200$ at nominal level 0.05 based on 1000 simulations.

| Model | Test | $U_{11}$ | $U_{21}$ | $U_{12}$ | $U_{22}$ | $U_{11}$ | $U_{21}$ | $U_{12}$ | $U_{22}$ |
|-------|------|----------|----------|----------|----------|----------|----------|----------|----------|
|       |      | IPW      |          |          |          |          |          |          | AIPW     |
|       |      | $U_{11}$ | $U_{21}$ | $U_{12}$ | $U_{22}$ | $U_{11}$ | $U_{21}$ | $U_{12}$ | $U_{22}$ |
| (Aux0): Kendall’s tau = 0 |
| $M_1$ | Size | 0.051    | 0.053    | 0.046    | 0.047    | 0.047    | 0.054    | 0.048    | 0.042    |
| $M_2$ | Power| 0.811    | 0.711    | 0.042    | 0.037    | 0.819    | 0.722    | 0.045    | 0.048    |
| $M_3$ |      | 0.987    | 0.971    | 0.059    | 0.054    | 0.991    | 0.979    | 0.064    | 0.045    |
| (Aux1): Kendall’s tau = 0.3 |
| $M_1$ | Size | 0.045    | 0.052    | 0.047    | 0.045    | 0.056    | 0.052    | 0.046    | 0.046    |
| $M_2$ | Power| 0.799    | 0.700    | 0.044    | 0.047    | 0.829    | 0.726    | 0.044    | 0.057    |
| $M_3$ |      | 0.986    | 0.970    | 0.062    | 0.049    | 0.991    | 0.979    | 0.059    | 0.046    |
| (Aux2): Kendall’s tau = 0.6 |
| $M_1$ | Size | 0.047    | 0.054    | 0.042    | 0.050    | 0.059    | 0.049    | 0.046    | 0.041    |
| $M_2$ | Power| 0.788    | 0.678    | 0.046    | 0.045    | 0.858    | 0.765    | 0.054    | 0.052    |
| $M_3$ |      | 0.987    | 0.968    | 0.063    | 0.048    | 0.996    | 0.992    | 0.061    | 0.047    |
Table 5: Empirical sizes and powers of the test statistics $T_1$ and $T_2$ for testing $H_{B0}$ under model (13) for $n = 1200$ at nominal level 0.05 based on 1000 simulations.

| Model | Test   | IPW $T_1$ | IPW $T_2$ | AIPW $T_1$ | AIPW $T_2$ |
|-------|--------|-----------|-----------|------------|------------|
|       |        | 0.047     | 0.061     | 0.048 0.064|            |
|       | N_1    | Size      | Power     |            |            |
|       |        | 0.766 0.664| 0.762 0.663|            |            |
|       | N_2    | 1.000 1.000| 1.000 1.000|            |            |
|       | (Aux0): Kendall’s tau = 0 |
|       |        | 0.047 0.064| 0.051 0.059|            |            |
|       | N_1    | Size      | Power     |            |            |
|       |        | 0.755 0.647| 0.775 0.671|            |            |
|       | N_2    | 1.000 1.000| 1.000 1.000|            |            |
|       | (Aux1): Kendall’s tau = 0.3 |
|       |        | 0.047 0.061| 0.051 0.066|            |            |
|       | N_1    | Size      | Power     |            |            |
|       |        | 0.746 0.638| 0.850 0.764|            |            |
|       | N_3    | 1.000 1.000| 1.000 1.000|            |            |
|       | (Aux2): Kendall’s tau = 0.6 |
Table 6: Estimation of covariate effects for the practice COVID-19 vaccine efficacy trial data set using IPW and AIPW methods for the cause V

|        | IPW          | AIPW         |
|--------|--------------|--------------|
|        | Est. | SE  | p-value | Est. | SE  | p-value |
| Cause V = 1 |      |     |        |      |     |        |
| Trt    | -2.439 | 0.269 | 0.000 | -2.461 | 0.161 | 0.000 |
| Highrisk | 2.175 | 0.135 | 0.000 | 2.003 | 0.082 | 0.000 |
| Age65+ | 1.123 | 0.115 | 0.000 | 1.198 | 0.076 | 0.000 |
| Minority | -0.159 | 0.117 | 0.175 | -0.049 | 0.080 | 0.540 |
| Female | -0.163 | 0.115 | 0.158 | -0.095 | 0.076 | 0.210 |
| Cause V = 2 |      |     |        |      |     |        |
| Trt    | -0.115 | 0.690 | 0.868 | -0.245 | 0.656 | 0.709 |
| Highrisk | 2.732 | 0.631 | 0.000 | 2.205 | 0.546 | 0.000 |
| Age65+ | 1.590 | 0.666 | 0.017 | 2.006 | 0.757 | 0.008 |
| Minority | 0.064 | 0.670 | 0.924 | 0.455 | 0.602 | 0.450 |
| Female | -0.054 | 0.643 | 0.933 | 0.086 | 0.644 | 0.894 |
| Cause V = 3 |      |     |        |      |     |        |
| Trt    | -0.842 | 0.533 | 0.114 | -0.841 | 0.532 | 0.114 |
| Highrisk | 2.765 | 0.628 | 0.000 | 2.769 | 0.627 | 0.000 |
| Age65+ | 1.350 | 0.459 | 0.003 | 1.341 | 0.460 | 0.004 |
| Minority | 0.674 | 0.466 | 0.148 | 0.643 | 0.469 | 0.171 |
| Female | 0.162 | 0.485 | 0.738 | 0.139 | 0.486 | 0.775 |

Est., the estimate of covariate coefficients; SE, the estimated standard error of the estimators of covariate coefficients; p-value pertaining to testing no covariate effect.
Table 7: Estimation of strain-specific vaccine efficacies for the practice COVID-19 VE trial data using IPW and AIPW methods for the cause $V$

|          | Est. | SE  | 95% LL | 95% UL | $U_{1j}$ | $p$-value | $U_{2j}$ | $p$-value |
|----------|------|-----|--------|--------|----------|-----------|----------|-----------|
| **IPW**  |      |     |        |        |          |           |          |           |
| $VE_1$   | 0.913| 0.024| 0.852  | 0.948  | -7.737   | $< 0.001$ | 59.868   | $< 0.001$ |
| $VE_2$   | 0.108| 0.615| -2.445 | 0.769  | 0.351    | 0.657     | 0.123    | 0.701     |
| $VE_3$   | 0.569| 0.230| -0.225 | 0.848  | -0.910   | 0.205     | 0.828    | 0.383     |
| **AIPW** |      |     |        |        |          |           |          |           |
| $VE_1$   | 0.915| 0.014| 0.883  | 0.938  | -13.041  | $< 0.001$ | 170.060  | $< 0.001$ |
| $VE_2$   | 0.217| 0.514| -1.834 | 0.784  | 0.171    | 0.583     | 0.0292   | 0.863     |
| $VE_3$   | 0.569| 0.230| -0.225 | 0.848  | -0.909   | 0.181     | 0.826    | 0.369     |

Est., the estimate of vaccine efficacies; SE, the estimated standard error of the estimators of VEs; 95% LL and 95% UL, lower limits (LL) and upper limits (UL) of 95% confidence intervals of vaccine efficacies.
Table 8: Estimation of VD for the practice COVID-19 vaccine efficacy trial data using IPW and AIPW methods for the cause V

|        | Est    | SE     | 95% LL | 95% UL |
|--------|--------|--------|--------|--------|
| IPW    |        |        |        |        |
| VD(2,1)| 10.216 | 7.607  | 2.374  | 43.967 |
| VD(1,2)| 0.098  | 0.073  | 0.023  | 0.421  |
| AIPW   |        |        |        |        |
| VD(2,1)| 9.176  | 6.678  | 2.204  | 38.210 |
| VD(1,2)| 0.109  | 0.079  | 0.026  | 0.454  |

Est., the estimate of VD; SE, the estimated standard error of the estimators of VD; 95% LL and 95% UL, lower limits (LL) and upper limits (UL) of 95% confidence intervals for VD.

Table 9: Results of hypothesis tests for the practice COVID-19 vaccine efficacy trial data using IPW and AIPW methods for the cause V

|        | $H_{A1}$ |        | $H_{A2}$ |        | $H_{B1}$ |        | $H_{B2}$ |        |
|--------|----------|--------|----------|--------|----------|--------|----------|--------|
|        | $U_1$    | $p$-value | $U_2$    | $p$-value | $T_1$    | $p$-value | $T_2$    | $p$-value |
| IPW    | -7.737   | < 0.001 | 59.991   | < 0.001 | 3.121    | 0.001   | 9.740    | 0.002   |
| AIPW   | -13.041  | < 0.001 | 170.089  | < 0.001 | 3.046    | 0.001   | 9.276    | 0.002   |

$H_{A1}$: $VE_j \geq 0.3$ with strict inequality for some $j \in \{1, 2\}$; $H_{A2}$: $VE_j \neq 0.3$ for some $j \in \{1, 2\}$; $H_{B1}$: $VE_1 > VE_2$; $H_{B2}$: $VE_1 \neq VE_2$.
Table 10: Estimation of covariate effects for the practice COVID-19 vaccine efficacy trial data set using IPW and AIPW methods for the cause $V^*$

| Cause $V^*$ = 1 | IPW | AIPW |
|-----------------|-----|------|
|                 | Est. | SE   | $p$-value | Est. | SE   | $p$-value |
| Trt             | -2.880 | 0.377 | 0.000 | -2.925 | 0.255 | 0.000 |
| Highrisk        | 2.087 | 0.155 | 0.000 | 1.976 | 0.113 | 0.000 |
| Age65+          | 1.339 | 0.137 | 0.000 | 1.372 | 0.107 | 0.000 |
| Minority        | -0.228 | 0.141 | 0.106 | -0.163 | 0.111 | 0.141 |
| Female          | -0.050 | 0.136 | 0.714 | -0.049 | 0.108 | 0.652 |

| Cause $V^*$ = 2 | IPW | AIPW |
|-----------------|-----|------|
|                 | Est. | SE   | $p$-value | Est. | SE   | $p$-value |
| Trt             | -2.791 | 0.638 | 0.000 | -2.934 | 0.730 | 0.000 |
| Highrisk        | 2.153 | 0.341 | 0.000 | 1.908 | 0.309 | 0.000 |
| Age65+          | 1.108 | 0.302 | 0.000 | 1.090 | 0.309 | 0.000 |
| Minority        | 0.016 | 0.326 | 0.960 | 0.162 | 0.304 | 0.595 |
| Female          | -0.256 | 0.307 | 0.406 | -0.049 | 0.325 | 0.880 |

| Cause $V^*$ = 3 | IPW | AIPW |
|-----------------|-----|------|
|                 | Est. | SE   | $p$-value | Est. | SE   | $p$-value |
| Trt             | -1.493 | 0.561 | 0.008 | -1.513 | 0.451 | 0.001 |
| Highrisk        | 2.373 | 0.511 | 0.000 | 2.081 | 0.372 | 0.000 |
| Age65+          | 0.359 | 0.388 | 0.356 | 0.643 | 0.328 | 0.050 |
| Minority        | -0.063 | 0.372 | 0.866 | 0.156 | 0.321 | 0.627 |
| Female          | -0.839 | 0.388 | 0.031 | -0.649 | 0.332 | 0.051 |

| Cause $V^*$ = 4 | IPW | AIPW |
|-----------------|-----|------|
|                 | Est. | SE   | $p$-value | Est. | SE   | $p$-value |
| Trt             | -0.635 | 0.502 | 0.206 | -0.651 | 0.402 | 0.105 |
| Highrisk        | 2.900 | 0.475 | 0.000 | 2.301 | 0.389 | 0.000 |
| Age65+          | 0.581 | 0.459 | 0.205 | 1.036 | 0.372 | 0.005 |
| Minority        | 0.077 | 0.425 | 0.856 | 0.443 | 0.365 | 0.225 |
| Female          | 0.099 | 0.430 | 0.817 | 0.403 | 0.409 | 0.325 |

| Cause $V^*$ = 5 | IPW | AIPW |
|-----------------|-----|------|
|                 | Est. | SE   | $p$-value | Est. | SE   | $p$-value |
| Trt             | -0.842 | 0.533 | 0.114 | -0.841 | 0.533 | 0.114 |
| Highrisk        | 2.765 | 0.628 | 0.000 | 2.769 | 0.627 | 0.000 |
| Age65+          | 1.350 | 0.459 | 0.003 | 1.341 | 0.460 | 0.004 |
| Minority        | 0.674 | 0.466 | 0.148 | 0.643 | 0.469 | 0.171 |
| Female          | 0.162 | 0.485 | 0.738 | 0.139 | 0.486 | 0.775 |

Est., the estimate of covariate coefficients; SE, the estimated standard error of the estimators of covariate coefficients; $p$-value pertaining to testing no covariate effect.
Table 11: Estimation of strain-specific vaccine efficacies for the practice COVID-19 VE trial data using IPW and AIPW methods for the cause $V^*$

|           | Est. | SE  | 95% LL | 95% UL | $H_{Aj1}: VE_j > 0.3$ | $H_{Aj2}: VE_j \neq 0.3$ |
|-----------|------|-----|--------|--------|----------------------|-------------------------|
|           |      |     |        |        | $U_{1j}$ | $p$-value | $U_{2j}$ | $p$-value |
| **IPW**   |      |     |        |        |          |            |          |            |
| $VE_1$    | 0.944| 0.021| 0.882  | 0.973  | -6.694   | 0.000      | 44.804   | 0.000      |
| $VE_2$    | 0.939| 0.039| 0.786  | 0.982  | -3.817   | 0.000      | 14.572   | 0.000      |
| $VE_3$    | 0.775| 0.126| 0.325  | 0.925  | -2.026   | 0.019      | 4.105    | 0.039      |
| $VE_4$    | 0.470| 0.266| -0.417 | 0.802  | -0.554   | 0.297      | 0.307    | 0.573      |
| $VE_5$    | 0.569| 0.230| -0.225 | 0.848  | -0.910   | 0.170      | 0.828    | 0.339      |
| **AIPW**  |      |     |        |        |          |            |          |            |
| $VE_1$    | 0.946| 0.014| 0.912  | 0.967  | -10.061  | 0.000      | 101.234  | 0.000      |
| $VE_2$    | 0.947| 0.039| 0.778  | 0.987  | -3.530   | 0.000      | 12.462   | 0.001      |
| $VE_3$    | 0.780| 0.099| 0.467  | 0.909  | -2.564   | 0.006      | 6.573    | 0.011      |
| $VE_4$    | 0.479| 0.210| -0.147 | 0.763  | -0.733   | 0.227      | 0.537    | 0.481      |
| $VE_5$    | 0.569| 0.230| -0.225 | 0.848  | -0.909   | 0.160      | 0.826    | 0.357      |

Est., the estimate of vaccine efficacies; SE, the estimated standard error of the estimators of VEs; 95% LL and 95% UL, lower limits (LL) and upper limits (UL) of 95% confidence intervals of vaccine efficacies
Table 12: Estimation of VD for the practice COVID-19 vaccine efficacy trial data using IPW and AIPW methods for the cause V^*

|               | Est. | SE  | 95% LL | 95% UL |
|---------------|------|-----|--------|--------|
| **IPW**       |      |     |        |        |
| VD(2,1)       | 1.092| 0.811| 0.255  | 4.679  |
| VD(3,2)       | 3.664| 3.123| 0.689  | 19.476 |
| VD(4,3)       | 2.359| 1.788| 0.534  | 10.418 |
| VD(1,2)       | 0.915| 0.679| 0.214  | 3.921  |
| VD(2,3)       | 0.273| 0.233| 0.051  | 1.451  |
| VD(3,4)       | 0.424| 0.321| 0.096  | 1.873  |
| **AIPW**      |      |     |        |        |
| VD(2,1)       | 0.991| 0.818| 0.196  | 5.000  |
| VD(3,2)       | 4.140| 3.680| 0.725  | 23.638 |
| VD(4,3)       | 2.367| 1.694| 0.582  | 9.623  |
| VD(1,2)       | 1.009| 0.833| 0.200  | 5.090  |
| VD(2,3)       | 0.242| 0.215| 0.042  | 1.379  |
| VD(3,4)       | 0.423| 0.302| 0.104  | 1.718  |

Est., the estimate of VD; SE, the estimated standard error of the estimators of VD; 95% LL and 95% UL, lower limits (LL) and upper limits (UL) of 95% confidence intervals for VD
Table 13: Results of hypothesis tests for the practice COVID-19 vaccine efficacy trial data using IPW and AIPW methods for the cause $V^*$

|       | $H_{A1}$ |       | $H_{A2}$ |       | $H_{B1}$ |       | $H_{B2}$ |
|-------|----------|-------|----------|-------|----------|-------|----------|
|       | $U_1$    | p-value | $U_2$    | p-value | $T_1$    | p-value | $T_2$    | p-value |
| IPW   | -6.694   | < 0.001| 63.787   | < 0.001| 0.119    | 0.012  | 3.616    | 0.283   |
| AIPW  | -10.061  | < 0.001| 120.806  | < 0.001| -0.011   | 0.015  | 4.003    | 0.236   |

$H_{A1}$: $VE_j \geq 0.3$ with strict inequality for some $j \in \{1,2,3,4\}$; $H_{A2}$: $VE_j \neq 0.3$ for some $j \in \{1,2,3,4\}$; $H_{B1}$: $VE_1 \geq VE_2 \geq VE_3 \geq VE_4$ with at least one strict inequality; $H_{B2}$: $VE_i \neq VE_j$ for at least one pair of $\{(i,j)| i < j, i, j \in \{1,2,3,4\}\}$