# Supplemental Appendix

## 1. Vaccine Efficacy

Let $S$ denote the time when vaccination takes place and $T$ denote the time when symptomatic COVID-19 develops; both times are measured in days from the start of the clinical trial (Figure 1). (We measure each participant's time to disease from the start of the trial rather than from their time of enrollment because the risk of disease depends on community transmission, which varies over the calendar time. Obviously, the two time scales are different under staggered enrollment.) In addition, let $X$ denote baseline risk factors (e.g., age, occupation, comorbidities). We specify that the hazard function of $T$ is related to $S$ and $X$ through the Cox regression model [1] with a time-varying vaccine effect

$$\lambda(t|S,X) = \lambda_0(t)v(t-S)^{I(t>S)}e^{\beta^{\mathrm{T}}X}, \tag{1}$$

where $\lambda_0(\cdot)$ is an arbitrary baseline hazard function, $v(\cdot)$ is a positive function characterizing the time-varying effect of vaccination, $\beta$ is a set of regression parameters representing the effects of baseline risk factors, and $I(\cdot)$ is the indicator function. Under this formulation, the baseline hazard rate varies over the calendar time; the effect of vaccine on the risk of disease depends on the time elapsed since vaccination, but not on the specific date of vaccination or on the baseline risk factors. (The latter restriction can be relaxed by applying the model separately to each sub-population of interest.)

Vaccine efficacy (VE) at time $t$ after vaccination is generally defined by $VE(t) = 1 - RR(t)$, where $RR(t)$ is some measure of relative risk at time $t$ comparing the vaccinated population to the unvaccinated population [2,3]. The most common measures of risk in vaccine trials are hazard rate and attack rate [3,4]. In our formulation, the relative hazard rate or hazard ratio at time $t$ is simply $v(t)$. The relative attack rate at time $t$ after vaccination when vaccination occurs at time $s$ is the ratio of the cumulative incidence of disease at time $t+s$ for individuals vaccinated at time $s$ compared with the unvaccinated:

$$\frac{\Pr(T \le t+s|T>s, S=s, X)}{\Pr(T \le t+s|T>s, S>t+s, X)} = \frac{1-\exp\{-e^{\beta^{\mathrm{T}}X}\int_s^{s+t} v(u-s)\lambda_0(u)du\}}{1-\exp\{-e^{\beta^{\mathrm{T}}X}\int_s^{s+t}\lambda_0(u)du\}},$$

which is approximately

$$\frac{\int_0^t v(u)\lambda_0(s+u)du}{\int_0^t \lambda_0(s+u)du} \tag{2}$$

when the incidence is low. (This condition holds for Covid-19 vaccine trials because the annualized incidence of symptomatic COVID-19 is less than 5%.) If $\lambda_0(\cdot)$ is approximately constant, then the ratio given in (2) can be written as $\overline{v}(t) = V(t)/t$, where

$$V(t) = \int_0^t v(u)du.$$

Clearly, $\overline{v}(t)$ is the average hazard ratio over the time period $(0,t]$.

Thus, we have two definitions of time-varying VE: one in terms of hazard rate

$$VE_h(t) = 1 - v(t), \tag{3}$$

and one in terms of attack rate

$$VE_a(t) = 1 - \overline{v}(t). \tag{4}$$

Note that the assumption of an approximately constant baseline hazard rate over time is needed in order to interpret $\overline{v}(t)$ as the ratio of the cumulative incidence but is not used in estimation. We will refer to $VE_a(t)$ as the VE in attack rate whether the baseline hazard rate is constant or not. We call $VE_h(t)$ the day-$t$ VE, which pertains to the instantaneous vaccine effect at time $t$, and call $VE_a(t)$ the $t$-day VE, which pertains to the cumulative vaccine effect over the time interval $(0, t]$. If the hazard ratio is constant over time, then the two definitions are equivalent. If the hazard ratio increases over time, then $VE_a(t)$ will be higher than $VE_h(t)$.

Suppose that the clinical trial enrolls a total of $n$ participants. For $i = 1, \ldots, n$, let $R_i$, $T_i$, $S_i$, $C_i$, and $X_i$ denote, respectively, the entry time, the time to symptomatic COVID-19, the time to vaccination, the time to loss to follow-up, and the baseline risk factors for the $i$th participant. The data consist of $(R_i, Y_i, \Delta_i, D_i, D_i S_i, X_i)$ $(i = 1, \ldots, n)$, where $Y_i = \min(T_i, C_i)$, $\Delta_i = I(T_i \le C_i)$, and $D_i = I(S_i \le Y_i)$.

We assume that $(R_i, S_i, C_i)$ are independent of $T_i$ conditional on $X_i$. The likelihood takes the form

$$\begin{aligned}
&\prod_{i=1}^{n} \left\{ \lambda_0(Y_i) e^{\beta^{\mathrm{T}} X_i} \right\}^{\Delta_i} v(\widetilde{Y}_i)^{D_i \Delta_i} \\
&\times \exp\left( -e^{\beta^{\mathrm{T}} X_i} \left[ (1 - D_i) \int_{R_i}^{Y_i} \lambda_0(t) dt + D_i \left\{ \int_{R_i}^{S_i} \lambda_0(t) dt + \int_{S_i}^{Y_i} \lambda_0(t) dV(t - S_i) \right\} \right] \right) \\
&= \prod_{i=1}^{n} \left\{ \lambda_0(Y_i) e^{\beta^{\mathrm{T}} X_i} \right\}^{(1-D_i)\Delta_i} \exp\left\{ -e^{\beta^{\mathrm{T}} X_i} \int_{R_i}^{Y_i^*} \lambda_0(t) dt \right\} \\
&\times \left[ \left\{ \lambda_0(Y_i) e^{\beta^{\mathrm{T}} X_i} v(\widetilde{Y}_i) \right\}^{\Delta_i} \exp\left\{ -e^{\beta^{\mathrm{T}} X_i} \int_{S_i}^{Y_i} \lambda_0(t) dV(t - S_i) \right\} \right]^{D_i},
\end{aligned}$$

where $\widetilde{Y}_i = Y_i - S_i$, and $Y_i^* = (1 - D_i) Y_i + D_i S_i = \min(Y_i, S_i)$. We approximate $\log \lambda_0(t)$ through splines with $m$ basis functions, $B_1(t), \ldots, B_m(t)$, such that $\log \lambda_0(t) \approx \sum_{k=1}^{m} \gamma_k B_k(t)$. Let $\theta = (\beta^{\mathrm{T}}, \gamma_1, \ldots, \gamma_m)^{\mathrm{T}}$, and $Z_i(t) = [X_i^{\mathrm{T}}, B_1(t), \ldots, B_m(t)]^{\mathrm{T}}$. We perform the nonparametric maximum likelihood estimation [5], in which $V(\cdot)$ is treated as a step function jumping at the time points $\widetilde{Y}_i$ with $D_i = \Delta_i = 1$. Thus, we maximize the objective function

$$\prod_{i=1}^{n} e^{(1-D_i)\Delta_i \theta^{\mathrm{T}} Z_i(Y_i)} \exp\left\{ -\int_{R_i}^{Y_i^*} e^{\theta^{\mathrm{T}} Z_i(t)} dt \right\} \left[ \left( e^{\theta^{\mathrm{T}} Z_i(Y_i)} V\{\widetilde{Y}_i\} \right)^{\Delta_i} \exp\left\{ -\int_0^{\widetilde{Y}_i} e^{\theta^{\mathrm{T}} Z_i(t+S_i)} dV(t) \right\} \right]^{D_i}, \tag{5}$$

where $V\{t\}$ is the jump size of $V(\cdot)$ at $t$.

We first maximize the objective function in (5) for fixed $\theta$ to yield

$$V(t) = \sum_{i=1}^{n} \frac{D_i \Delta_i I(\widetilde{Y}_i \le t)}{S^{(0)}(\theta; \widetilde{Y}_i)}. \tag{6}$$

Here and in the sequel, $S^{(k)}(\theta; y) = \sum_{j=1}^{n} D_j I(\widetilde{Y}_j \ge y) e^{\theta^{\mathrm{T}} Z_j(y+S_j)} Z_j(y+S_j)^{\otimes k}$, where $a^{\otimes 0} = 1$, $a^{\otimes 1} = a$, and $a^{\otimes 2} = a a^{\mathrm{T}}$ for a column vector $a$. After plugging (6) into (5), we obtain the

profile likelihood for $\theta$. Differentiating the profile log-likelihood with respect to $\theta$ yields the estimating function

$$\sum_{i=1}^{n}\left\{(1-D_i)\Delta_i Z_i(Y_i)-\int_{R_i}^{Y_i^*} e^{\theta^{\mathrm{T}}Z_i(t)}Z_i(t)dt\right\}+\sum_{i=1}^{n}D_i\Delta_i\left\{Z_i(Y_i)-\frac{S^{(1)}(\theta;\widetilde{Y}_i)}{S^{(0)}(\theta;\widetilde{Y}_i)}\right\}.$$

Denote the resulting estimator of $\theta$ by $\widehat{\theta}$. Replacing $\theta$ in (6) by $\widehat{\theta}$ yields the estimator of $V(t)$

$$\widehat{V}(t)=\sum_{i=1}^{n}\frac{D_i\Delta_i I(\widetilde{Y}_i\le t)}{S^{(0)}(\widehat{\theta};\widetilde{Y}_i)},$$

which is reminiscent of the Breslow estimator [6] for the cumulative baseline hazard function under the standard Cox model. We then estimate $VE_a(t)$ through equation (4).

Using counting-process martingale theory and other mathematical arguments [7,8], we can show that $\widehat{V}(\cdot)$ is consistent and asymptotically normal. In addition, the covariance between $\widehat{V}(t_1)$ and $\widehat{V}(t_2)$ can be consistently estimated by $n^{-1}\sum_{i=1}^{n}W_i(t_1)W_i(t_2)$, where

$$W_i(t)=D_i\left[\frac{\Delta_i I(\widetilde{Y}_i\le t)}{S^{(0)}(\widehat{\theta};\widetilde{Y}_i)}-\sum_{j=1}^{n}\frac{D_j\Delta_j I\{\widetilde{Y}_j\le\min(t,\widetilde{Y}_i)\}e^{\widehat{\theta}^{\mathrm{T}}Z_i(\widetilde{Y}_j+S_i)}}{S^{(0)}(\widehat{\theta};\widetilde{Y}_j)^2}\right]$$

$$-\sum_{j=1}^{n}\frac{D_j\Delta_j I(\widetilde{Y}_j\le t)S^{(1)}(\widehat{\theta};\widetilde{Y}_j)^{\mathrm{T}}}{S^{(0)}(\widehat{\theta};\widetilde{Y}_j)^2}\,Q_i,$$

and

$$Q_i=\left[\sum_{i=1}^{n}\int_{R_i}^{Y_i^*}e^{\widehat{\theta}^{\mathrm{T}}Z_i(t)}Z_i(t)^{\otimes 2}dt+\sum_{i=1}^{n}D_i\Delta_i\left\{\frac{S^{(2)}(\widehat{\theta};\widetilde{Y}_i)}{S^{(0)}(\widehat{\theta};\widetilde{Y}_i)}-\frac{S^{(1)}(\widehat{\theta};\widetilde{Y}_i)^{\otimes 2}}{S^{(0)}(\widehat{\theta};\widetilde{Y}_i)^2}\right\}\right]^{-1}$$

$$\times\left[(1-D_i)\Delta_i Z_i(Y_i)-\int_{R_i}^{Y_i^*}e^{\widehat{\theta}^{\mathrm{T}}Z_i(t)}Z_i(t)dt+D_i\Delta_i\left\{Z_i(Y_i)-\frac{S^{(1)}(\widehat{\theta};\widetilde{Y}_i)}{S^{(0)}(\widehat{\theta};\widetilde{Y}_i)}\right\}\right.$$

$$\left.-D_i\sum_{j=1}^{n}\frac{D_j\Delta_j I(\widetilde{Y}_i\ge\widetilde{Y}_j)e^{\widehat{\theta}^{\mathrm{T}}Z_i(\widetilde{Y}_j+S_i)}}{S^{(0)}(\widehat{\theta};\widetilde{Y}_j)}\left\{Z_i(\widetilde{Y}_j+S_i)-\frac{S^{(1)}(\widehat{\theta};\widetilde{Y}_j)}{S^{(0)}(\widehat{\theta};\widetilde{Y}_j)}\right\}\right].$$

These results can be used to construct confidence intervals for $VE_a(t)$. Specifically, we first construct the confidence intervals for $\log\{V(t)\}$ and then transform them to $VE_a(t)$. We can also construct simultaneous confidence bands for $VE_a(\cdot)$ [8].

We estimate $v(\cdot)$ by applying a local linear smoother to the jump sizes of $\widehat{V}(\cdot)$. The jump size of $\widehat{V}(\cdot)$ at $\widetilde{Y}_i$ is given by $\widehat{v}_i=D_i\Delta_i/S^{(0)}(\widehat{\theta};\widetilde{Y}_i)$. For any $t$, we fit a local linear regression model and estimate its intercept $A(t)$ and slope $B(t)$ by solving the equation

$$\sum_{i=1}^{n}K_{b_n}(\widetilde{Y}_i-t)\begin{bmatrix}1\\ \widetilde{Y}_i-t\end{bmatrix}\left\{\widehat{v}_i-A(t)-B(t)(\widetilde{Y}_i-t)\right\}=0,$$

where $K_{b_n}(x)=b_n^{-1}K(x/b_n)$, $K(x)=(2\pi)^{-1/2}e^{-x^2/2}$, and $b_n$ is a data-adaptive bandwidth. We let $b_n=cR_D/n_D^{1/5}$, where $c$ is a tuning parameter, $R_D$ is the range of the observed event

times, and $n_D$ is the number of disease cases [9]. Denote the resulting estimator of $A(t)$ by $\widehat{A}(t)$. We then estimate $v(t)$ by

$$\widehat{v}(t) = \widehat{A}(t) \sum_{i=1}^{n} K_{b_n}(\widetilde{Y}_i - t)$$

and estimate $\mathrm{VE_h(t)}$ according to equation (3). We let the tuning parameter $c$ lie between 0.1 and 1.0. A smaller value of $c$ makes $\widehat{v}(t)$ less biased but more variable, whereas a larger value of $c$ generates a more smooth estimate of the $\mathrm{VE_h}$ curve.

Finally, we define the VE in attack rate over the time interval $(t_1, t_2]$ by

$$VE_a(t_1, t_2) = 1 - \frac{V(t_2) - V(t_1)}{t_2 - t_1}.$$

The fraction on the right-hand side is the average hazard ratio over the time period $(t_1, t_2]$. We estimate $V(t_2) - V(t_1)$ by $\widehat{V}(t_2) - \widehat{V}(t_1)$, which is normally distributed with variance $\mathrm{Var}\{\widehat{V}(t_1)\} + \mathrm{Var}\{\widehat{V}(t_2)\} - 2\ \mathrm{Cov}\{\widehat{V}(t_1), \widehat{V}(t_2)\}$. We then construct the confidence intervals for $VE_a(t_1, t_2)$ based on the log-transformation.

*Remark.* Durham et al. [2] considered a special case of model (1) in which all participants are vaccinated at approximately the same time (such that $S$ can be set 0 for all participants) and estimated the time-varying hazard ratio by smoothing the residuals from the standard Cox model with a constant hazard ratio. If community transmission is constant over time, then one can estimate the incidence rate in the vaccine group by using the number of cases among the participants who have been vaccinated for the same amount of time and assess waning VE by comparing the estimates of relative incidence rates for successive time periods. In COVID-19 vaccine trials, the enrollment period is relatively long compared with the study duration, and community transmission varies considerably over time. Thus, it is necessary to adopt two different time scales: time since study initiation for the disease endpoint and time since vaccination for the vaccine effect.

## 2. Simulation Studies

We assumed that 40,000 participants entered the study at a constant rate over four months, i.e., $R \sim \mathrm{Uniform}(0, 4)$. We created a composite baseline risk score $X$, which takes values 1, 2, 3, 4, and 5 with equal probability. At study entry, half of the participants were assigned to vaccine and half to placebo. The statistically optimal design would be to maintain the original vaccine and placebo groups until the end of the study; we refer to this design as Plan A. We also considered three blinded crossover designs, under which placebo participants receive vaccine and vaccine participants receive placebo at the time of crossover, and all participants are followed until the end of the study or the time of analysis, which was set to be 10.5 months. The three blinded crossover designs are as follows:

Plan B. Crossover occurs at month $(11 - X + G)$, where $G$ follows the exponential distribution with mean of 0.5 month.

Plan C. 20% of participants follow Plan A and 80% follow Plan B.

Plan D. Crossover occurs at month $6 + G$, where $G$ follows the exponential distribution with mean of 0.5 month.

Plan C mimics a scenario where all participants are offered the option of crossover, but a small percentage (20%) choose to stay on the original assignments.

In addition, we considered four unblinded crossover designs:

Plan B'. Crossover occurs at month $(11.5 - X)$.

Plan C'. 20% of participants follow Plan A and 80% follow Plan B'.

Plan D'. Crossover occurs at month 6.5.

Plan D". Crossover occurs at the same time as Plan D.

Under unblinded crossover, participants are notified of their original assignments at the time of crossover, and placebo participants receive the vaccine soon after. In practice, only placebo participants would cross over, since there is no need to give placebo to vaccine recipients after unblinding. In Plans B'–D", the time of crossover is the time of unblinding rather than the time when placebo participants actually receive the vaccine. Because participants might change their behavior upon discovering their original treatment assignments, we discarded the follow-up data collected after unblinding by censoring each participant's time to disease at their time of unblinding. This strategy avoids bias due to behavioral confounding at the cost of reduced statistical efficiency.

We generated the event time $T$ from model (1) with $\beta = 0.2$,

$$\log \lambda_0(t) = -5.93 + 0.1t - 0.3(t-7)_+,$$

and

$$\log v(t) = a + bt, \quad t > 0,$$

where $t_+ = t$ if $t > 0$ and 0 otherwise, and $a$ and $b$ were chosen to achieve the desired 5-month and 10-month $\text{VE}_\text{a}$. We censored $T$ at the time of unblinding under Plans B'–D".

For each simulated dataset, we estimated $\log \lambda_0(t)$ using a piece-wise constant function with 20 pieces placed at the equal quantiles of the observed event times. We then estimated $V(t)$ using the proposed method and estimated $VE_a(t)$ according to equation (4). In addition, we estimated $v(t)$ through local linear regression with tuning parameter $c = 0.1$ and estimated $VE_h(t)$ according to equation (3). For comparison, we also fit the standard Cox proportional hazards model that includes $X$ and time-dependent covariate $I(S < t)$ with a constant hazard ratio and estimated VE by 1 minus the estimated hazard ratio of the time-dependent covariate. The results are reported in the main text.

## 3. Sensitivity Analysis

We suggest reporting the E-value [10] as a summary measure of the evidence against the null hypothesis $H_0 : VE(t) \leq 0$. The E-value is the minimum strength of association on the risk ratio scale, i.e, $RR(t) = 1 - VE(t)$, that an unmeasured confounder would need to have with both vaccination status and disease outcome in order to fully explain away a specific observed VE. Let $\widehat{RR}(t)$ be the estimate of $RR(t)$, and let $UL(t)$ be the upper limit of the 95% confidence interval for $RR(t)$. Then the E-value for $\widehat{RR}(t)$ is given by

$$e(t) = \frac{1 + \sqrt{1 - \widehat{RR}(t)}}{\widehat{RR}(t)},$$

provided that $\widehat{RR}(t) < 1$. In addition, the E-value for $UL(t)$ is computed as 1 if $UL(t) \geq 1$ and as

$$e_{UL}(t) = \frac{1 + \sqrt{1 - UL(t)}}{UL(t)}$$

otherwise. E-values near one suggest weak support for a causal inference, and greater E-values provide increasing evidence for causality.

Suppose, for example, that $\widehat{RR}(t) = 0.50$, with 95% confidence interval $(0.08, 0.75)$. Then $e(t) = 3.4$, meaning that the result of $\widehat{RR}(t)$ being less than one could be explained away by an unmeasured confounder associated with both vaccination status and disease by a risk ratio of 3.4-fold each after accounting for the vector $X$ of measured confounders, but not by a weaker unmeasured confounder. In addition, $e_{UL}(t) = 2$, which is the strength of unmeasured confounding at which statistical significance for $VE(t) > 0$ would be lost. These two E-values judge how confident we can be that $VE(t)$ truly exceeds 0, accounting for potential unmeasured confounding due to unblinding and for sampling variability.

We can provide a conservative estimate of $VE(t)$ that accounts for potential unmeasured confounding [11]. Let $RR_{UD}(t)$ be the maximum risk ratio for disease when comparing any two categories of the unmeasured confounder $U$, within either the vaccinated group or the unvaccinated group, conditional on the vector $X$ of observed covariates, and let $RR_{EU}(t)$ be the maximum risk ratio for any specific level of the unmeasured confounder $U$ when comparing the vaccinated and unvaccinated individuals. Of note, $RR_{UD}(t)$ quantifies the importance of the unmeasured confounder $U$ for disease, and $RR_{EU}(t)$ quantifies how imbalanced the vaccinated and unvaccinated groups are in the unmeasured confounder $U$. We define the bias or bounding factor

$$B(t) = \frac{RR_{UD}(t)RR_{EU}(t)}{RR_{UD}(t) + RR_{EU}(t) - 1}.$$

Then a conservative (lower bound) estimate of the VE is given by $1 - \widehat{RR}(t)B(t)$, and a conservative confidence interval is obtained by multiplying the lower and upper limits of the confidence interval for $RR(t)$ by $B(t)$.

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