1 Supplementary Materials for Vaccine Efficacy at a Point in Time

In this supplement we derive $\mathrm{VE}_{PI}(s)$ and $\mathrm{VE}_{PVL}(s)$ while allowing for time-varying vaccine efficacy on infection and the distribution of post infection viral load. We also allow for a nonconstant hazard in an interval prior to s and define $\mathrm{VE}_{PI}(s)$ and $\mathrm{VE}_{PVL}(s)$ under a local constant hazard assumption.

1.1 $VE_{PI}(s)$

Let the discrete time hazard for infection be

$$\lambda(s;Z) = \lambda_0(s)\exp(Z\theta(t)),$$

where s is the number of days since vaccination. Let $S(s;Z) = P(T > s|Z)$. Then consider discrete time, where $s = 1, 2, \dots$ are positive integers. We use the following approximation,

$$P(T = s|Z) \quad \approx \quad \lambda(s|Z) \tag{1}$$

Approximation 1 assumes (i) $\lambda(s;Z)$ is small, and (ii) $S(s-1;Z) \approx 1$.

Approximation 1 justification:

$$\begin{aligned} P(T = s; Z) &= S(s-1;Z) - S(s;Z) \\ &= \exp\left(-\sum_{j=1}^{s-1}\lambda(j;Z)\right) - \exp\left(-\sum_{j=1}^{s}\lambda(j;Z)\right) \\ &= S(s-1;Z)\left\{1 - \exp\left(-\lambda(s;Z)\right)\right\} \end{aligned}$$

For $\lambda(s)$ small, by a Taylor series approximation, we have $1-\exp(-\lambda(s)) \approx \lambda(s)$, giving

$$P(T = s;Z) \quad \approx \quad S(s-1;Z)\lambda(s;Z)$$

and if $S(s-1;Z) \approx 1$, then $P(T = s;Z) \approx \lambda(s;Z)$.

Let $p_Z(d,t)$ be the probability that the infection acquired at day t post vaccination has a duration of d days. Let $\mathcal{T}_s = \{s-M+1, s-M+2, \dots, s\}$. Because the maximum duration of an infection is M,

$$P(Y(s) = 1|Z) = P(Y(s) = 1 \quad \& \quad T \in \mathcal{T}_s|Z).$$

We are interested in the ratio, $P(Y(s) = 1|Z = 1)/P(Y(s) = 1|Z = 0)$, which is

$$\frac{P(Y(s) = 1 \quad \& \quad T \in \mathcal{T}_s|Z = 1)}{P(Y(s) = 1 \quad \& \quad T \in \mathcal{T}_s|Z = 0)} \quad = \quad \frac{P(T \in \mathcal{T}_s|Z = 1)}{P(T \in \mathcal{T}_s|Z = 0)} \times \frac{P(Y(s) = 1|T \in \mathcal{T}_s, Z = 1)}{P(Y(j) = 1|T \in \mathcal{T}_s, Z = 0)}$$

This is the ratio of infection probabilities over $s-M+1, \dots, s$ times the ratio of the probabilities that an infection that starts during $s-M+1, \dots, s$ is detected at time s.

When the infection probability is independent of s, the first term reduces to $\exp(\theta)$ and the second term reduces to Δ_1/Δ_0. But for time dependent vaccine efficacy, it is more complicated.

Consider $P(Y(s)=1|Z)$ in discrete time,

$$
\begin{aligned}
P(Y(s)=1 \quad \& \quad T \in \mathcal{T}_s|Z) &= \sum_{t=s-M+1}^{s} P(T=t|Z)P(D \geq s-t+1|T=t,Z) \\
&= \sum_{t=s-M+1}^{s} P(T=t|Z) \sum_{d=s-t+1}^{M} p_Z(d,t) \\
&\approx \sum_{t=s-M+1}^{s} \lambda(t|Z) \sum_{d=s-t+1}^{M} p_Z(d,t) \\
&= \sum_{d=1}^{M} \sum_{t=s-d+1}^{s} \lambda(t|Z) p_Z(d,t) \qquad (2)
\end{aligned}
$$

where the penultimate step uses (1). Using (2), we get

$$P(Y(s)=1|T \in \mathcal{T}_j, Z=1) \approx \frac{\sum_{t=s-M+1}^{s} \lambda_0(t)\exp(\theta(t)) \sum_{d=s-t+1}^{M} p_1(d,t)}{\sum_{t=s-M+1}^{s} \lambda_0(t)\exp(\theta(t))} \equiv \pi_1(s).$$

For $Z=0$, the value of $p_0(d,t)$ does not depend on t, since t represents the time from vaccination to infection, and for placebo vaccinations, this should have no effect. Thus, we let $p_0(d,t)=p_0(d)$, and using (2), we get

$$P(Y(s)=1|T \in \mathcal{T}_s, Z=0) \approx \frac{\sum_{t=s-M+1}^{s} \lambda_0(t) \sum_{d=s-t+1}^{M} p_0(d)}{\sum_{t=s-M+1}^{s} \lambda_0(t)} \equiv \pi_0(s).$$

Note that even though $p_0(d,t)$ does not depend on t, $\pi_0(s)$ still depends on s, since the $\lambda_0(t)$ for $t \in \{s-M+1,\ldots,s\}$ give weights for a weighted average of sums of $p_0(d)$ values. Using (1), we get

$$\frac{P(T \in \mathcal{T}_s|Z=1)}{P(T \in \mathcal{T}_s|Z=0)} \approx \frac{\sum_{t=s-M+1}^{s} \lambda_0(t)\exp\{\theta(t)\}}{\sum_{t=s-M+1}^{s} \lambda_0(t)} \equiv \exp\{\bar{\theta}_\lambda(s)\}. \qquad (3)$$

where $\bar{\theta}_\lambda(s)$ is defined implicitly.

Thus,

$$\frac{P(Y(s)=1|Z=1)}{P(Y(s)=1|Z=0)} \approx \exp\{\bar{\theta}_\lambda(s)\}\frac{\pi_1(s)}{\pi_0(s)}. \qquad (4)$$

Under the assumption that $\lambda_0(t)$ is approximately constant for $t \in \mathcal{T}_t$, we have

$$\exp\{\bar{\theta}_\lambda(s)\} = \frac{\sum_{t=s-M+1}^{s} \lambda_0 \exp\{\theta(t)\}}{\sum_{t=s-M+1}^{s} \lambda_0} = \sum_{t=s-M+1}^{s} \frac{\exp\{\theta(t)\}}{M} = \exp\{\bar{\theta}(s)\}.$$

Furthermore

$$\pi_0(s) = \frac{\sum_{t=s-M+1}^{s} \lambda_0 \sum_{d=s-t+1}^{M} p_0(d))}{\sum_{t=s-M+1}^{s} \lambda_0} = \pi_0 = \Delta_0/M$$

Thus under the constant $\lambda_0(t)$ assumption we have

$$\frac{P(Y(s)=1|Z=1)}{P(Y(s)=1|Z=0)} \approx \exp\{\bar{\theta}(s)\}\frac{\Delta_1(s)}{\Delta_0}. \tag{5}$$

where $\Delta_1(s) = M\pi_1(s)$

1.2 $VE_{PVL}(s)$

Now we turn to defining $VE_{PVL}(s)$. Similar to the derivation of approximation (2), we get an approximation for the mean length-biased viral load,

$$\begin{aligned}
E(V(s,B,D)|Z) &\approx \sum_{d=1}^{M}\sum_{t=s-d+1}^{s} \lambda(t|Z)p_Z(d,t)\nu_Z(s-t+1,d,t) \\
&= \left\{\sum_d\sum_t \lambda(t|Z)\right\}\left\{\frac{\sum_d\sum_t \lambda(t|Z)p_Z(d,t)}{\sum_d\sum_t \lambda(t|Z)}\right\}\left\{\frac{\sum_d\sum_t \lambda(t|Z)p_Z(d,t)\nu_Z(s-t+1,d,t)}{\sum_d\sum_t \lambda(t|Z)p_Z(d,t)}\right\} \\
&= \left\{\sum_d\sum_t \lambda(t|Z)\right\}\{\pi_Z(s)\}\{\nu_Z(s)\}
\end{aligned}$$

where the summation indices over d and t remain the same as in the first line, and $\pi_Z(s)$ and $\nu_Z(s)$ are defined implicitly. Then

$$\begin{aligned}
1-\frac{E(V(s,B,D)|Z=1)}{E(V(s,B,D)|Z=0)} &\approx 1-\frac{\sum_{d=1}^{M}\sum_{t=s-d+1}^{s}\lambda_0(t)\exp(\theta(t))p_1(d,t)\nu_1(s-t+1,d,t)}{\sum_{d=1}^{M}\sum_{t=s-d+1}^{s}\lambda_0(t)p_0(d)\nu_0(s-t+1,d,t)} \\
&= 1-\exp\left\{\bar{\theta}_\lambda(s)\right\}\frac{\pi_1(s)}{\pi_0(s)}\frac{\nu_1(s)}{\nu_0(s)}.
\end{aligned}$$

Under the assumption that the baseline hazards are approximately constant in $t \in \mathcal{T}_t$, we have,

$$\nu_Z(s) = \left\{\frac{\sum_d\sum_t \exp\{Z\theta(t)\}p_Z(d,t)\nu_Z(s-t+1,d,t)}{\sum_d\sum_t \exp\{Z\theta(t)\}p_Z(d,t)}\right\}$$

where $\nu_0(s)=\nu_0$. Using the results of the previous section we have $\exp\{\bar{\theta}_\lambda(s)\} = \exp\{\bar{\theta}(s)\}$ $\pi_1(s) = \Delta_1(s)/M$ and $\pi_0(s) = \Delta_0/M$. This gives our representation of $VE_{PVL}(s)$,

$$1-\exp\left\{\bar{\theta}(s)\right\}\frac{\Delta_1(s)}{\Delta_0}\frac{\nu_1(s)}{\nu_0}. \tag{6}$$