# Web-based Supplementary Materials for Sieve Analysis Using the Number of Infecting Pathogens by Follmann and Huang.

## Web Appendix A: Development and asymptotics for WEE

Our approach follows that of Follmann & Huang (2015) where estimating equations were derived from a single empirical process that jumped by $X$ when infection occurred. In that work $X$ was the total number of clonally unique infecting pathogens. Here we apply that approach marginally for each of the $f = 1, \ldots, F$ different pathogens and then combine the associated estimating equations. The flavor of the approach is similar to competing risks as multiple types of events are considered, though different as simultaneous infections by multiple pathogens are allowed.

We assume that at each exposure an independent $\boldsymbol{X} = (X_1, \ldots, X_F)$ is drawn and a (terminal) infection occurs and follow-up stops if $X_+ = \sum_{f=1}^{F} X_f > 0$. Let $T$ be the time to infection and $C$ the common time to censoring for all pathogens. Moreover, define $Y = \min(T, C)$, $\delta = I(T \leqslant C)$ and $N(t) = \delta I(Y \leqslant t)$. Next define $\boldsymbol{X}^A$ as the vector of counts at infection if $\delta = 1$ and $\mathbf{0}$ otherwise.

We define $\boldsymbol{W}^E$ as covariates that effect exposure (e.g. bed nets for malaria or condoms for HIV) and $\boldsymbol{W}_f^X$ as covariates that impact $X_f$ (e.g. similarity of $f$ to the immunogen times the vaccine indicator, innate immunity, vaccine indicator times the time since randomization). Note $\boldsymbol{W}_f^X$ implicitly includes $Z$. Let $\boldsymbol{W}^X = (\boldsymbol{W}_1^X, \ldots, \boldsymbol{W}_F^X)$ and define $\boldsymbol{W} = (\boldsymbol{W}^E, \boldsymbol{W}^X)$.

We assume that the intensity of exposure is given by

$$\omega(t \mid \boldsymbol{W}) = \omega(t) \exp(\boldsymbol{\theta}' \boldsymbol{W}^E),$$

where $\omega(t)$ is an unspecified baseline exposure intensity function. It follows that the hazard for time to infection is given by

$$\omega(t) \exp(\boldsymbol{\theta}' \boldsymbol{W}^E) P(X_+ > 0 | \boldsymbol{W}).$$

We next assume that the mean of $X_f$ at time $t$, conditional on exposure, satisfies the proportional mean model

$$\begin{aligned} E(X_f \mid \boldsymbol{W}) &= E(X_f \mid \boldsymbol{W}_f^X) \\ &= \exp\{\beta_f(t) + \boldsymbol{\phi}'\boldsymbol{W}_f^I + \boldsymbol{\psi}' Z \boldsymbol{V}_f\},\ f = 1, \ldots, F. \end{aligned}$$

Note that $\beta_f(t)$ allows arbitrary changes in the placebo mean for pathogen $f$ over time. Implicitly, $X_f$ depends on $t$ but for simplicity we do not reflect this in our notation. The covariates $\boldsymbol{W}_f^I$ reflect generic effects that impact both the placebo and vaccine means, such as innate immunity, while $\boldsymbol{V}_f$ reflects the distance from the vaccine to the immunogen—as such it only applies to the vaccine group. It can be shown that the mean of $X_f$ conditional on infection is proportional to the unconditional mean

$$E(X_f | X_+ > 0, \boldsymbol{W}) = E(X_f|\boldsymbol{W})/P(X_+ > 0|\boldsymbol{W}).$$

Next define the empirical process for feature $f$ as

$$X_f^A dN_f(t) = X_f^A dN(t) I(X_f > 0).$$

With the above specifications, we can derive the mean of $X_{fi}^A dN_{fi}(t)$ for subject $i = 1, \ldots, n$ and feature $f = 1, \ldots, F$. This will allow us to derive unbiased estimating equations using the mean zero empirical processes $X_f^A dN_f(t) - E\{X_f^A dN_f(t)\}$. Now,

$$\begin{aligned} &E\{X_{fi}^A dN_{fi}(t) \mid \boldsymbol{W}_i\} \\ &= \sum_{x=0}^{\infty} x P\{X_{fi}^A = x, dN_{fi}(t) = 1 \mid \boldsymbol{W}_i\} \\ &= \sum_{x=0}^{\infty} x P\{X_{fi}^A = x \mid dN_{fi}(t) = 1, \boldsymbol{W}_i\} P\{dN_{fi}(t) = 1 \mid \boldsymbol{W}_i\} \\ &= E(X_{fi} \mid \boldsymbol{W}_{fi}^X)/P(X_{+i} > 0 \mid \boldsymbol{W}_{fi}^X)\omega(t)\exp(\boldsymbol{\theta}'\boldsymbol{W}_i^E) P(X_{+i} > 0 | \boldsymbol{W}_{fi}^X) P(Y_i \geqslant t \mid \boldsymbol{W}_i) dt \\ &= E(X_{fi} \mid \boldsymbol{W}_{fi}^X)\omega(t)\exp(\boldsymbol{\theta}'\boldsymbol{W}_i^E) P(Y_i \geqslant t \mid \boldsymbol{W}_i) dt \\ &= \exp\{\beta_f(t)\}\omega(t)\exp(\boldsymbol{\phi}'\boldsymbol{W}_{fi}^I + \boldsymbol{\psi}' Z_i \boldsymbol{V}_{fi} + \boldsymbol{\theta}'\boldsymbol{W}_{fi}^E) P(Y_i \geqslant t \mid \boldsymbol{W}_i) dt \\ &= \lambda_f(t)\exp(\boldsymbol{\phi}'\boldsymbol{W}_{fi}^I + \boldsymbol{\psi}' Z_i \boldsymbol{V}_{fi} + \boldsymbol{\theta}'\boldsymbol{W}_i^E) P(Y_i \geqslant t \mid \boldsymbol{W}_i) dt, \end{aligned}$$

where $\lambda_f(t) = \exp\{\beta_f(t)\}\omega(t)$ is the instantaneous mean function for a person in the placebo group with covariates $\boldsymbol{W}_{fi}^I = \mathbf{0}$ and $\boldsymbol{W}_i^E = \mathbf{0}$. We regard this as a nuisance function. Because some covariates might impact both exposure (and be in $\boldsymbol{W}_i^E$) and the mean of $X_f$ given exposure (and be in $\boldsymbol{W}_{fi}^I$) we will define $\boldsymbol{W}_{fi}^u$ as the unique elements of $\boldsymbol{W}_{fi}^I, Z_i\boldsymbol{V}_i, \boldsymbol{W}_i^E$. We will only be able to estimate the overall effect (i.e. $\theta + \phi$ ) for such covariates.

With the expectation of $E\{X_{fi}^A dN_i(t)\}$ determined above, we can now define $F$ mean zero stochastic processes

$$M_{fi}(t) = \int_0^\tau X_{fi}^A dN_{fi}(u) - \int_0^\tau \lambda_f(u) \exp(\boldsymbol{\alpha}'\boldsymbol{W}_{fi}^u) I(Y_i \geqslant u) du,$$

for $f = 1, \ldots, F$. In the above, $\tau$ is a constant satisfying $\tau < \sup\{t : P(Y > t) > 0\}$. It can be shown that

$$E\left\{\sum_{i=1}^n \int_0^t dM_{fi}(u)\right\} = 0 \quad \text{for all } t \in [0, \tau], \tag{1}$$

$$E\left\{\sum_{i=1}^n \int_0^\tau \boldsymbol{W}_{fi}^u dM_{fi}(u)\right\} = 0, \tag{2}$$

for $f = 1, \ldots, F$. The first equality corresponds to $F$ equations, while the last equality corresponds to $F \times p$ equations, where $p = \dim(\boldsymbol{\alpha})$.

Define $\Lambda_f(t) = \int_0^\tau \lambda_f(s)ds$. Solving the equation $\sum_{i=1}^n \int_0^\tau dM_{fi}(u) = 0$ for each $t$ and each $f$ yields

$$\widehat{\Lambda}_f(t) = \sum_{i=1}^n \int_0^t \frac{X_{fi}^A dN_{fi}(u)}{\sum_{k=1}^n \exp(\boldsymbol{\alpha}'\boldsymbol{W}_{fk}^u) I(Y_k \geqslant u)}, \tag{3}$$

with the convention that $0/0 = 0$. Note that if there are no events of type $f$, then $\widehat{\Lambda}_f(t)$ is zero. Replacing $\Lambda_f(t)$ with (3) in the estimating equations $\sum_{i=1}^n \int_0^\tau \boldsymbol{W}_{fi}^u dM_{fi}(u) = 0$ eliminates the nuisance functions $\lambda_1(), \ldots, \lambda_F()$ and yields the $F \times p$ estimating equations

$$\sum_{i=1}^n \int_0^\tau X_{fi}^A \left\{\boldsymbol{W}_{fi}^u - \frac{\sum_{j=1}^n \boldsymbol{W}_{fj}^u \exp(\boldsymbol{\alpha}'\boldsymbol{W}_{fj}^u) I(Y_j \geqslant u)}{\sum_{k=1}^n \exp(\boldsymbol{\alpha}'\boldsymbol{W}_{fk}^u) I(Y_k \geqslant u)}\right\} dN_{fi}(u) = \mathbf{0}. \tag{4}$$

We can form a reduced set of $p$ estimating equations to efficiently estimate $\boldsymbol{\alpha}$ by summing over $f$

$$U(\boldsymbol{\alpha}) = \sum_{i=1}^{n} \left[ \sum_{f=1}^{F} \int_0^{\tau} X_{fi}^A \left\{ \boldsymbol{W}_{fi}^u - \frac{\sum_{j=1}^n \boldsymbol{W}_{fj}^u \exp(\boldsymbol{\alpha}' \boldsymbol{W}_{fj}^u) I(Y_j \geqslant u)}{\sum_{k=1}^n \exp(\boldsymbol{\alpha}' \boldsymbol{W}_{fk}^u) I(Y_k \geqslant u)} \right\} dN_{fi}(u) \right] = \mathbf{0}. \quad (5)$$

We call the solution to (5) the weighted estimating equations (WEE) estimator, $\hat{\boldsymbol{\alpha}}$.

Define $\Gamma = -n^{-1} E\{\partial U(\boldsymbol{\alpha})/\partial \boldsymbol{\alpha} \mid_{\boldsymbol{\alpha}=\boldsymbol{\alpha}_0}\}$, where the derivative is given by

$$\begin{aligned} \frac{\partial U(\boldsymbol{\alpha})}{\partial \alpha} &= \sum_{i=1}^{n} \sum_{f=1}^{F} \int_0^{\tau} X_{fi}^A \left[ \left\{ \frac{\sum_{j=1}^n \boldsymbol{W}_{fj}^u \exp(\boldsymbol{\alpha}' \boldsymbol{W}_{fj}^u) I(Y_j \geqslant u)}{\sum_{k=1}^n \exp(\boldsymbol{\alpha}' \boldsymbol{W}_{fk}^u) I(Y_k \geqslant u)} \right\}^{\otimes 2} \right. \\ &\quad \left. - \frac{\sum_{j=1}^n \boldsymbol{W}_{fj}^{u\otimes 2} \exp(\boldsymbol{\alpha}' \boldsymbol{W}_{fj}^u) I(Y_j \geqslant u)}{\sum_{k=1}^n \exp(\boldsymbol{\alpha}' \boldsymbol{W}_{fk}^u) I(Y_k \geqslant u)} \right] dN_{fi}(u). \end{aligned}$$

Moreover, define

$$U_i(\boldsymbol{\alpha}) = \sum_{f=1}^{F} \int_0^{\tau} X_{fi}^A \left\{ \boldsymbol{W}_{fi}^u - \frac{\sum_{j=1}^n \boldsymbol{W}_{fj}^u \exp(\boldsymbol{\alpha}' \boldsymbol{W}_{fj}^u) I(Y_j \geqslant u)}{\sum_{k=1}^n \exp(\boldsymbol{\alpha}' \boldsymbol{W}_{fk}^u) I(Y_k \geqslant u)}, \right\} dN_{fi}(u)$$

and $\Omega = \text{var}\{U_i(\boldsymbol{\alpha}_0)\}$. By a Taylor series expansion and applying the standard argument, we can show that $\sqrt{n}(\hat{\boldsymbol{\alpha}} - \boldsymbol{\alpha}_0)$ converges to a multivariate normal distribution with mean zero and variance-covariance matrix $\Gamma^{-1}\Omega\Gamma^{-1}$.

Web Appendix B: WEE and product estimator performance in different settings

A small simulation was conducted to examine the performance of the WEE and product estimators under different scenarios including time constant and time varying $F_Z()$ and the presence and absence of subject level heterogeneity. For each simulated trial $n = 100$ volunteers are randomized to vaccine or placebo and the gap times between exposures are generated as independent exponentials with parameter $\omega = 0.5$. The trial is simultaneous entry with a common follow-up of 3. Individual effects, $\exp(b_i)$, are generated as Gamma with mean 1 and variance $\sigma^2_{exp(b)} = 0$ or 2. Following exposure for person $i$, a bivariate negative binomial is drawn where $X_{i1}, X_{i2}|b_i$ has mean $E(X_{fi}|b_i) = \exp\{b_i + S_p \times \alpha_1 + \alpha_2 Z_i + \alpha_3 I(f = 2) + \alpha_4 I(f = 2)Z_i\}$. We set $S_1 = +1$ or -1 for exposures times in the first half of follow-up, i.e. $T$ in (0, 1.5), and set $S_2 = +1$ or -1 for exposures times in the second half of follow-up, i.e. $T$ in (1.5,3). Thus $S_1, S_2$=(+1,+1) corresponds to a time constant pathogen mean while $S_1, S_2$=(+1,-1) has fewer pathogens in period 2 and $S_1, S_2$= (-1,+1) has fewer in period 1. We specified $\alpha_1 = 1.0$ and $\alpha_3 = -0.7$ so type $f = 2$ infections are less common than $f = 1$, $\alpha_2 = -1.5$ so there was a vaccine effect, and $\alpha_4 = -0.5$ so there was a sieve effect. We also evaluated a null case with no vaccine effect on either pathogen $\boldsymbol{\alpha} = (1.0, 0, -0.7, 0)$.

If $X_{+i} = X_{1i} + X_{2i} > 0$, the person is counted as infected and the time of infection and $\boldsymbol{X}_{fi}$ recorded. If $X_{+i} = X_{1i} + X_{2i} = 0$, another gap time to the next exposure is drawn and another bivariate negative binomial $X_{1i}, X_{2i}$ generated as above until the associated $X_{+i} > 0$ or the sum of the gap times exceeds 3 and the individual is censored. Under this model and conditional on $b_i, S_p$ we have $VE_{M1} = 1 - \exp(\alpha_2)$ and $VE_{M2} = 1 - \exp(\alpha_2 + \alpha_4)$, so that $\alpha_4$ describes the sieve effect. We consider both WEE and product estimators of $\text{VE}_{Mf}$. Each scenario was simulated 10,000 times. Table 1 presents the results. Note that the WEE estimator should be unbiased for any $S_1, S_2$ with $\sigma^2_{\exp(b)} = 0$ while the product estimator

should be unbiased for any $S_1, S_2 = 1, 1$ with $\sigma^2_{\exp(b)} = 0$. The other scenarios correspond to mis-specifications.

Scanning the $\alpha_4$ columns reveals that both the WEE and product methods are essentially unbiased for the sieve effect for all scenarios. For the first half of the table for non-null $\boldsymbol{\alpha}$ we see that the WEE is relatively unbiased for $\alpha_2$ for all scenarios except $S_1, S_2$= (-1,+1) where it has modest bias of at most 10% when $\exp(b_i)$ has variance 2 . In contrast, the product estimator is badly biased for $\alpha_2$ for all values of $S_1, S_2$ when $\sigma^2_{\exp(b)} = 2$. For the bottom half of the table for non-null $\boldsymbol{\alpha}$ we see that the WEE estimator is unbiased for all scenarios while the product estimator is substantially biased for $\alpha_2$, except when it is correctly specified with $\sigma^2_{\exp(b)} = 0$ and $S_1, S_2 = (1, 1)$. The results for $\alpha_2 + \alpha_4$ i.e. the transformed $VE_2$ are similar.

[Table 1 about here.]

Web Appendix C: EWCR and Active Surveillance estimates of $\mathrm{VE}_{If}$ are different

In this appendix we further explore the difference between the WCR and Product estimates of $\mathrm{VE}_{If}$. For simplicity we assume that exposure times are exponential and construct explicit estimators. Let $\omega$ be the (constant) risk of exposure. Following exposure, counts $X_1, X_2$ are drawn from $F(x_1, x_2|z)$ where $z$ identifies the vaccine group. Thus the times to infection are exponentially distributed with parameter $\omega P(X_1 + X_2 > 0)$.

For a single resample, the WCR estimator of the exponential parameter for the time to infection by a pathogen with feature $f$ in group $z$ is given by

$$\hat{\lambda}_{fz} = \frac{\sum_{i=1}^{n} I(X_{fi} > 0) I(Z_i = z) B_{fi}}{T_z},$$

where $T_z = \sum_{i=1}^{n} Y_i I(Z_i = z)$ and $(B_{i1}, B_{i2}) = (1,0)$ or $(0,1)$ is distributed as a single multinomial with probabilities $(p_{1i}, p_{2i}) = \{X_{1i}/(X_{1i} + X_{2i}), X_{2i}/(X_{1i} + X_{2i})\}$, respectively. It is easy to see that as the number of resamples goes to infinity $B_{fi} \to p_{fi}$, so the exhaustive WCR estimator is

$$\widehat{\lambda}_{fz}^{EWCR} = \frac{\sum_{i=1}^{n} I(X_{fi} > 0) I(Z_i = z) p_{fi}}{T_z}.$$

Asymptotically on $n$

$$\begin{aligned}
\widehat{\lambda}_{fz}^{EWCR} &= \frac{\sum_{i=1}^{n} I(X_{fi} > 0) I(Z_i = z) p_{fi}}{T_z} && (6)\\
&\to \omega P(X_+ > 0 | Z = z) \times && (7)\\
&\quad \{P(X_{f'} < X_f | Z = z, X_+ > 0) + 1/2 P(X_1 = X_2 | Z = z, X_+ > 0)\} && (8)\\
&= \omega \{P(X_{f'} < X_f, X_+ > 0 | Z = z) + 1/2 P(X_1 = X_2, X_+ > 0 | Z = z)\} && (9)
\end{aligned}$$

Thus

$$1 - \widehat{VE}_{fi}^{EWCR} \to 1 - \frac{P(X_{f'} < X_f, X_+ > 0 | Z = 1) + 1/2 P(X_1 = X_2, X_+ > 0 | Z = 1)}{P(X_{f'} < X_f, X_+ > 0 | Z = 0) + 1/2 P(X_1 = X_2, X_+ > 0 | Z = 0)}.$$

This can be viewed as the estimate of vaccine efficacy for the first infecting pathogen with censoring of subsequent clonally distinct pathogens.

The product estimate of $\mathrm{VE}_{If}$ under the exponential assumption is given by the estimate

of overall vaccine efficacy on infection times a ratio of conditional infection probabilities.

$$\begin{aligned} 1-\widehat{\mathrm{VE}}_{If}^{Prod} &= 1-\frac{\frac{\sum_{i=1}^{n} I(X_{+i}>0)I(Z_i=1)}{T_1}}{\frac{\sum_{i=1}^{n} I(X_{+i}>0)I(Z_i=0)}{T_0}} \times \frac{\hat{P}(X_f>0|X_+>0,Z=1)}{\hat{P}(X_f>0|X_+>0,Z=0)} \\ &\to 1-\frac{\omega P(X_+>0|Z=1)}{\omega P(X_+>0|Z=0)}\frac{P(X_f>0|Z=1,X_+>0)}{P(X_f>0|Z=0,X_+>0)} \\ &= 1-\frac{P(X_f>0|Z=1)}{P(X_f>0|Z=0)}. \end{aligned}$$

This is an estimate of the marginal vaccine efficacy. It is clear that $\widehat{VE}_{If}^{Prod}$ and $\widehat{VE}_{If}^{WCR}$ estimate different parameters in general, though both converge to 0 on the null $F_{Z=0}(x_1,x_2) = F_{Z=1}(x_1,x_2)$.

A small simulation was done to explore the behavior of the two estimators under exponential exposures and time constant $F_Z$ corresponding to that of Appendix 2 with $S_1, S_2 = +,+$ and $\sigma^2_{\exp(b)} = 0$. Note that the data are generated under a bivariate negative binomial model for the counts but here we fit a model for infection. As such we use $\alpha_{1I}, \alpha_{2I}$ for these infection parameters to distinguish from the mean parameters $\boldsymbol{\alpha} = (\alpha_1, \alpha_2, \alpha_3, \alpha_4)$.

We see that for the non-null case with $\boldsymbol{\alpha} = (1.0, -1.5, -0.7, -0.5)$ the product estimator is farther from zero and has smaller variance than the EWCR counterpart. The relative efficiency for the sieve effect is 3.48. For the null case with $\boldsymbol{\alpha} = (1, 0, -0.7, 0)$ both estimators are unbiased for the null sieve effect. The ratio of sample variances is 3.54. For simplicity, we did not evaluate the WEE in this setting, but simulations have shown that it is virtually identically to the product estimator for this setting with exponential times to infection and time constant $F_Z$

[Table 2 about here.]

**Table 1**

*Simulated performance of the WEE and product estimators of mean parameters. 100 volunteers are randomized to vaccine(Z=1) or placebo (Z=0), gap times between exposures are exponential, and the number of infecting pathogens per exposure is a bivariate negative binomial with* $E(X_{fi}|b_i) = \exp(b_i + S_p \times \alpha_1 + \alpha_2 Z_i + \alpha_3 I(f=2) + \alpha_4 I(f=2)Z_i)$, *where* $\exp(b_i)$ *is Gamma with mean 1 and variance* $\sigma^2_{\exp(b)}$. *The coefficient* $S_p$ *is either +1 or -1 with* $S_1$ *for* $\boldsymbol{X}$ *drawn in the first half of follow-up (i.e exposure times in (0,C/2) ) and* $S_2$ *applying to* $\boldsymbol{X}$ *drawn for exposure times in (C/2,C). Sample means and variances of the parameter estimates are reported in successive rows.*

| | | | | WEE | | | Product | | |
|---|---|---|---|---|---|---|---|---|---|
| $\sigma^2_{\exp(b)}$ | $S_1S_2$ | $\overline{X>0}$ | $P(X>0)$ | $\alpha_2$ | $\alpha_2+\alpha_4$ | $\alpha_4$ | $\alpha_2$ | $\alpha_2+\alpha_4$ | $\alpha_4$ |
| $\boldsymbol{\alpha}$= (1,-1.5,-0.7,-0.5) | | | | | | | | | |
| 0 | ++ | 2.052 | 0.602 | -1.505 | -2.018 | 0.513 | -1.509 | -2.023 | 0.513 |
| | | | | 0.044 | 0.091 | 0.088 | 0.044 | 0.090 | 0.088 |
| 0 | +- | 1.883 | 0.500 | -1.507 | -2.033 | 0.525 | -1.379 | -1.905 | 0.526 |
| | | | | 0.061 | 0.137 | 0.137 | 0.080 | 0.155 | 0.136 |
| 0 | -+ | 1.864 | 0.497 | -1.507 | -2.025 | 0.518 | -1.520 | -2.039 | 0.519 |
| | | | | 0.066 | 0.141 | 0.141 | 0.048 | 0.120 | 0.136 |
| 2 | ++ | 2.723 | 0.469 | -1.528 | -2.049 | 0.521 | -0.966 | -1.488 | 0.522 |
| | | | | 0.092 | 0.148 | 0.099 | 0.127 | 0.185 | 0.098 |
| 2 | +- | 2.483 | 0.380 | -1.524 | -2.055 | 0.531 | -0.808 | -1.340 | 0.532 |
| | | | | 0.129 | 0.216 | 0.154 | 0.165 | 0.251 | 0.153 |
| 2 | -+ | 2.046 | 0.404 | -1.360 | -1.894 | 0.533 | -0.918 | -Inf | Inf |
| | | | | 0.133 | 0.271 | 0.211 | 0.129 | NaN | NaN |
| $\boldsymbol{\alpha}$ = (1,0 ,-0.7,0) | | | | | | | | | |
| 0 | ++ | 2.427 | 0.735 | -0.002 | -0.000 | -0.002 | -0.003 | -0.000 | -0.002 |
| | | | | 0.035 | 0.044 | 0.029 | 0.035 | 0.044 | 0.029 |
| 0 | +- | 2.179 | 0.636 | -0.001 | 0.001 | -0.003 | 0.226 | 0.229 | -0.003 |
| | | | | 0.045 | 0.059 | 0.040 | 0.064 | 0.077 | 0.039 |
| 0 | -+ | 2.064 | 0.618 | -0.004 | 0.000 | -0.004 | -0.129 | -0.125 | -0.005 |
| | | | | 0.052 | 0.068 | 0.048 | 0.033 | 0.048 | 0.042 |
| 2 | ++ | 3.377 | 0.565 | 0.002 | 0.004 | -0.002 | 0.585 | 0.587 | -0.002 |
| | | | | 0.085 | 0.093 | 0.029 | 0.118 | 0.126 | 0.029 |
| 2 | +- | 3.016 | 0.471 | -0.002 | -0.004 | 0.002 | 0.782 | 0.780 | 0.002 |
| | | | | 0.113 | 0.128 | 0.041 | 0.150 | 0.164 | 0.039 |
| 2 | -+ | 2.357 | 0.488 | 0.004 | 0.006 | -0.002 | 0.394 | 0.394 | -0.000 |
| | | | | 0.122 | 0.143 | 0.058 | 0.117 | 0.135 | 0.050 |

**Table 2**

*Simulated performance of the EWCR and product estimates of $VE_I$ under exponential exposure times. Simulation setup is the same as for the $S_1, S_2 = (1, 1)$ and $\sigma^2_{\exp(b)}$=0 scenarios of Table 1 in Appendix 2. We parameterize $VE_{If} = 1 - \exp\{\alpha_{1I} + \alpha_{2I} I(f = 2)\}$, so that $\alpha_{2I}$ reflects the sieve effect. Sample means and variances of the estimated $\alpha_I$s are reported. RE is the relative efficiency of the product method to EWCR for the estimate of $\alpha_{2I}$. For the null scenario this is the ratio of sample variances. For the non-null setting, since the two methods estimate different parameters, we form $\mathcal{Z}^2_{PROD}/\mathcal{Z}^2_{EWCR}$, where $\mathcal{Z}$ is the sample average divided by the sample standard deviation.*

| | | Product | | | EWCR | | | |
|---|---|---|---|---|---|---|---|---|
| $\sigma^2_{exp(b)}$ | $S_1S_2$ | $\alpha_{1I}$ | $\alpha_{1I}+\alpha_{2I}$ | $\alpha_{2I}$ | $\alpha_{1I}$ | $\alpha_{1I}+\alpha_{2I}$ | $\alpha_{2I}$ | RE |
| $\boldsymbol{\alpha}$= (1,-1.5,-0.7,-0.5) | | | | | | | | |
| 0 | ++ | -0.727 | -1.514 | 0.787 | -0.456 | -0.974 | 0.518 | 3.48 |
| | | 0.036 | 0.081 | 0.071 | 0.038 | 0.094 | 0.107 | |
| $\boldsymbol{\alpha}$ = (1,0 ,-0.7,0) | | | | | | | | |
| 0 | ++ | -0.002 | -0.001 | -0.001 | -0.002 | -0.001 | -0.001 | 3.54 |
| | | 0.027 | 0.034 | 0.011 | 0.030 | 0.043 | 0.039 | |