Inference on Treatment Effect Modification by Marker Response in a Baseline Surrogate Measure Three-Phase Sampling Design

Michal Juraska\textsuperscript{1}

Joint work with: Peter B. Gilbert\textsuperscript{1,2} and Ying Huang\textsuperscript{1,2}

\textsuperscript{1} Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center
\textsuperscript{2} Department of Biostatistics, University of Washington

September 24–26, 2018
Motivation: two Phase 3 Dengvaxia trials

- Two randomized placebo-controlled Phase 3 dengue vaccine trials in 31144 children
- Harmonized trial designs
- Vaccine/placebo administered at months 0, 6, and 12
- Primary clinical endpoint: symptomatic virologically confirmed dengue (VCD) between months 13 and 25
- Asian trial: $\hat{VE} = 56.5\%$ (95% CI, 43.8 to 66.4)
- Latin American trial: $\hat{VE} = 60.8\%$ (95% CI, 52.0 to 68.0)

Does average neutralizing antibody titer, measured in the vaccine group at month 13, modify $\text{VE}(13-25)$ against VCD in participants free of VCD through month 13?
Motivation: two Phase 3 Dengvaxia trials

Three-phase case-cohort sampling design

- Baseline serum samples collected from a random sample (subcohort \( S \)) of
  - \( \approx 10\% \) of all participants in the Asian trial
  - \( \approx 20\% \) of all participants in the Latin American trial
- Month 13 serum samples collected from all participants

\[ \downarrow \]

- **Phase 1**: baseline covariates (e.g., demographics) in all participants
- **Phase 2**: biomarker \( S \) (NAb titer) at month 13 in a subset of subcohort \( S \) and in all post-month 13 VCD cases
- **Phase 3**: biomarker’s baseline value \( S_b \) only in a subset of subcohort \( S \)
Motivation: two Phase 3 Dengvaxia trials

- $S_b$ and $S$ highly correlated, making $S_b$ ideal as a baseline immunogenicity predictor\(^1\) (baseline surrogate measure\(^2\))
- All alternative EML and PS methods\(^3\) require that $S_b$ be measured from all vaccine recipients with $S$ measured
  \[\Rightarrow\] These methods would discard data from 80–90% of VCD endpoint cases in the vaccine group!

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\(^1\) Follmann (2006); Gilbert and Hudgens (2008)
\(^2\) Gabriel and Gilbert (2014)
\(^3\) Gilbert and Hudgens (2008); Huang and Gilbert (2011); Huang, Gilbert, and Wolfson (2013); Gabriel and Gilbert (2014); Huang (2017)
Notation

- $Z$ treatment indicator
- $X = (X_1, \ldots, X_k)$ baseline covariate vector
- $S$ discrete or continuous univariate biomarker at fixed time $\tau$ after randomization
- $S_b$ baseline value of the biomarker
- $\epsilon$ and $\delta$ indicators of measured $S$ and $S_b$
- $Y$ indicator of clinical endpoint after $\tau$
- $Y^{\tau}$ indicator of clinical endpoint at or before $\tau$
- $Y^{\tau}(Z), \epsilon(Z), S(Z), Y(Z)$ potential outcomes of $Y^{\tau}, \epsilon, S, Y$ under $Z$

To evaluate $S(1)$ as a modifier of treatment effect on $Y$, $S$ needs to be measured prior to $Y$. 
⇒ Analysis restricted to participants with $Y^{\tau} = 0$. 
Three-phase case-cohort sampling design

Phase 1: $Z, X, Y^\tau, Y$ measured in all randomized participants

Phase 2 (classic case-cohort design [Prentice, 1986]):

- Bernoulli sample $S$ at baseline
- $S$ measured at $\tau$ in
  - a subset of $S$ with $Y^\tau = 0$, and
  - all (or almost all) cases ($Y = 1$) with $Y^\tau = 0$

Phase 3:

- $S_b$ measured at baseline in a subset of $S$ with $Y^\tau = 0$

Consequence: $S_b$ measured only in those cases with $Y^\tau = 0$ that were sampled into $S$
Identifiability assumptions

1. \((Z_i, X_i, \delta_i, \delta_i S_{b,i}, Y_i^T(0), Y_i^T(1), \epsilon_i(0), \epsilon_i(0) S_i(0), \epsilon_i(1), \epsilon_i(1) S_i(1), Y_i(0), Y_i(1)), i = 1, \ldots, n, \text{ i.i.d. with no drop-out}\)

2. Standard identifiability assumptions†
   a. Stable unit treatment value assumption (SUTVA) and consistency:
      \((Y_i^T(0), Y_i^T(1), \epsilon_i(0), \epsilon_i(0) S_i(0), \epsilon_i(1), \epsilon_i(1) S_i(1), Y_i(0), Y_i(1)) \perp \perp Z_j, j \neq i, \text{ and } (V_i(Z_i), \epsilon_i(Z_i) S_i(Z_i), Y_i(Z_i)) = (V_i, \epsilon_i S_i, Y_i)\)
   b. Ignorable treatment assignment:
      \(Z_i \perp \perp (\delta_i, \delta_i S_{b,i}, Y_i^T(0), Y_i^T(1), \epsilon_i(0), \epsilon_i(0) S_i(0), \epsilon_i(1), \epsilon_i(1) S_i(1), Y_i(0), Y_i(1)) | X_i\)
   c. Equal early clinical risk:
      \(P\{Y_i^T(0) = Y_i^T(1)\} = 1^*\)

* Henceforth all unconditional and conditional probabilities of \(Y(z) = 1\) implicitly condition on \(Y^T(1) = Y^T(0) = 0\).
† Gilbert and Hudgens (2008); Huang and Gilbert (2011); Huang, Gilbert, and Wolfson (2013); Gabriel and Gilbert (2014); Huang (2017)
Modeling assumptions

3. \( P\{ Y(z) = 1 | X, S(z) \} \) follows a GLM for \( z = 0, 1 \)
   ▶ For \( z = 0 \), it replaces “placebo structural risk” assumption of all EML and PS methods\(^\dagger\) that \( P\{ Y(0) = 1 | X, S(1) \} \) follows a GLM

4. Conditional independence:
   \( P\{ Y(0) = 1 | X, S(0), S(1) \} = P\{ Y(0) = 1 | X, S(0) \} \)

5. Time constancy:
   \( f(s_1 | X = x, S(0) = s_0) = \tilde{f}(s_1 | X = x, S_b = s_0) \) for all \((s_1, x, s_0)\)

\(^\dagger\) Gilbert and Hudgens (2008); Huang and Gilbert (2011); Huang, Gilbert, and Wolfson (2013); Gabriel and Gilbert (2014); Huang (2017)
Estimand of interest: mCEP($s_1$)

- Overall causal treatment effect on $Y$
  \[ CE = h(\mathbb{P}\{Y(1) = 1\}, \mathbb{P}\{Y(0) = 1\}) \]
- $h(x, y)$ a known contrast function
- Marginal causal effect predictiveness curve*,†
  \[ mCEP(s_1) = h(\mathbb{P}\{Y(1) = 1|S(1) = s_1\}, \mathbb{P}\{Y(0) = 1|S(1) = s_1\}) \]
- Principal stratification estimand‡ \(\Rightarrow\) measures causal treatment effect on $Y$ for a subgroup with $S(1) = s_1$
- Examples:
  \[ h(x, y) = 1 - x/y \text{ multiplicative risk reduction} \]
  \[ h(x, y) = y - x \text{ attributable risk} \]

* Gilbert and Hudgens (2008)
† If $S$ is continuous, this definition abuses notation for simplicity of exposition.
‡ Frangakis and Rubin (2002)
Estimation of $\text{mCEP}(s_1)$

$\rho_z(s_1) := P\{Y(z) = 1 | S(1) = s_1\}$ for $z = 0, 1$

$m\text{CEP}(s_1) = h\{p_1(s_1), p_0(s_1)\}$

Estimate $p_1(s_1)$ via the specified GLM, accounting for case-cohort sampling of $S$

- E.g., using the `tps` function in the `ROSDesign` package
Estimation of $m\text{CEP}(s_1)$

$$p_0(s_1) = \int P\{Y(0) = 1|X = x, S(0) = s_0\} \times$$

$$\times \frac{f(s_1|s_0, x)g(s_0|x)r(x)}{m(s_1)} d^{k+1}(s_0, x),$$

$$m(s_1) = \int f(s_1|s_0, x)g(s_0|x)r(x) d^{k+1}(s_0, x)$$

- Estimate $P\{Y(0) = 1|X = x, S(0) = s_0\}$ via the specified GLM, accounting for case-cohort sampling of $S$
- Estimate $f(s_1|S_0 = s_0, X = x)$ by estimating $\tilde{f}(s_1|S_b = s_0, X = x)$ via nonparametric kernel smoothing, accounting for the three-phase sampling design
  - E.g., using the npcdensbw, npcdens, npudensbw, npudens functions in the R np package
- Estimate $g(s_0|x)$ and $r(x)$ analogously
Interval estimation of mCEP($s_1$)

Bootstrap procedures designed to construct

1. pointwise Wald-type CI for mCEP($s_1$) for a given $s_1$
2. simultaneous Wald-type CI for \{mCEP($s_1$), $s_1 \in S\}$, for an arbitrary subset $S$ of the support of $S(1)$

- Cases and controls sampled separately in each bootstrap sample
Simultaneous Wald-type CI for \( \{ \text{mCEP}(s_1), s_1 \in S \} \)

- \( \eta(s_1) := \eta\{ \text{mCEP}(s_1) \} \) a “symmetrizing” transformation
  - \( h(x, y) = 1 - x/y \Rightarrow \eta\{ h(x, y) \} = \log\{1 - h(x, y)\} \)
- \( \hat{\eta}(s_1) = \eta\{ \hat{\text{mCEP}}(s_1) \} \)
- \( U^{(b)} := \sup_{s_1 \in S} |\hat{\eta}^{(b)}(s_1) - \hat{\eta}(s_1)| / SE^{*}\{\hat{\eta}(s_1)\} \)
- \( c_\alpha^* \) empirical quantile of \( U^{(b)} \), \( b = 1, \ldots, B \), at probability \( 1 - \alpha \)
- \( (1 - \alpha) \times 100\% \) CI as \( \eta^{-1}(\cdot) \) transformation of
  \[
  (l_{\alpha}^n(s_1), u_{\alpha}^n(s_1)) = \hat{\eta}(s_1) \pm c_\alpha^* SE^{*}\{\hat{\eta}(s_1)\}.
  \]
Hypothesis tests via simultaneous estimation method of Roy and Bose (1953) for

1. $H_0^1: m\text{CEP}(s_1) \equiv CE$ for all $s_1 \in S$
2. $H_0^2: m\text{CEP}(s_1) \equiv c$ for all $s_1 \in S_1 \subseteq S$ and a known constant $c \in \mathbb{R}$
3. $H_0^3: m\text{CEP}_1(s_1) = m\text{CEP}_2(s_1)$ for all $s_1 \in S_1 \subseteq S$, where $m\text{CEP}_1$ and $m\text{CEP}_2$ are each associated with either a different biomarker (measured in the same units) or a different endpoint or both
4. $H_0^4: m\text{CEP}(s_1 | X = 1) = m\text{CEP}(s_1 | X = 0)$ for all $s_1 \in S_1 \subseteq S$, where $X$ is a baseline dichotomous phase 1 covariate of interest included in $X$
Tests of $H^1_0$ and $H^2_0$

$H^1_0 : m\text{CEP}(s_1) \equiv CE$ for all $s_1 \in S$
$H^2_0 : m\text{CEP}(s_1) \equiv c$ for all $s_1 \in S_1 \subseteq S$ and a known constant $c \in \mathbb{R}$

$U^{(b)}_{\eta}(S, a) := \sup_{s_1 \in S} \left| \hat{\eta}^{(b)}(s_1) - \eta(a) \right| / SE^*\{\hat{\eta}(s_1)\}, \ a \in \mathbb{R}$

Regions of rejection of $H^1_0$ and $H^2_0$ at significance level $\alpha$:

$U_1 := \sup_{s_1 \in S} \left| \hat{\eta}(s_1) - \eta(\text{CE}) \right| / SE^*\{\hat{\eta}(s_1)\} > c^*_1 \alpha$
$U_2 := \sup_{s_1 \in S_1} \left| \hat{\eta}(s_1) - \eta(c) \right| / SE^*\{\hat{\eta}(s_1)\} > c^*_2 \alpha$

$c^*_1 \alpha$ and $c^*_2 \alpha$ empirical quantiles of $U^{(b)}_{\eta}(S, \text{CE})$ and $U^{(b)}_{\eta}(S_1, c), \ b = 1, \ldots, B$, at probability $1 - \alpha$

Two-sided p-values as empirical probabilities that $U^{(b)}_{\eta}(S, \text{CE}) > U_1$ and $U^{(b)}_{\eta}(S_1, c) > U_2$
Test of $H^3_0$

$H^3_0 :$ mCEP$_1(s_1) =$ mCEP$_2(s_1)$ for all $s_1 \in S_1 \subseteq S$, where mCEP$_1$ and mCEP$_2$ are each associated with either a different biomarker or a different endpoint or both.

- $\theta(s_1) := \eta\{\text{mCEP}_1(s_1)\} - \eta\{\text{mCEP}_2(s_1)\}$
- $U_\theta^{(b)} := \sup_{s_1 \in S_1} |\hat{\theta}^{(b)}(s_1)| / SE^*\{\hat{\theta}(s_1)\}$
- Region of rejection of $H^3_0$ at significance level $\alpha$:

$$U_3 := \sup_{s_1 \in S_1} |\hat{\theta}(s_1)| / SE^*\{\hat{\theta}(s_1)\} > c^*_3\alpha$$

- $c^*_3\alpha$ empirical quantile of $U_\theta^{(b)}$, $b = 1, \ldots, B$, at probability $1 - \alpha$
- Two-sided p-value as empirical probability that $U_\theta^{(b)} > U_3$
Test of $H_0^4$

$H_0^4 : \text{mCEP}(s_1|X = 1) = \text{mCEP}(s_1|X = 0)$ for all $s_1 \in S_1 \subseteq S$, where $X$ is a baseline dichotomous phase 1 covariate of interest

▶ Estimates of $\text{mCEP}(s_1)$ in subgroups $X = 1$ and $X = 0$ are independent

▶ Test of $H_0^4$ identical to that of $H_0^3$ except

\[
SE^* \{\hat{\theta}(s_1)\} = \left\{ SE^* \left[ \eta \{ \text{mCEP}(s_1|X = 1) \} \right] + \right. \\
+ SE^* \left[ \eta \{ \text{mCEP}(s_1|X = 0) \} \right] \right\}^{1/2}
\]
Simulation setup

Three-phase case-cohort sampling design

Phase 1:
- $N = 5000$ randomized at 1:1 ratio to $Z = 1$ or 0 and followed for a binary $Y$ (assumed to occur after $\tau$ at which $S(Z)$ is measured)

Phase 2:
- Bernoulli sample $S$ at baseline with sampling probability $\pi = 0.1, 0.25, \text{ and } 0.5$
- $S(Z)$ measured at $\tau$ in $S$ and in all cases ($Y = 1$)

Phase 3:
- $S_b$ measured at baseline in $S$ only, i.e., $S_b$ missing in cases not included in $S$
Simulation setup

\[
\begin{pmatrix}
S_b \\
S(0) \\
S(1)
\end{pmatrix}
\sim
\mathcal{N}
\begin{pmatrix}
2 \\
2 \\
3
\end{pmatrix},
\begin{pmatrix}
1 & 0.9 & 0.7 \\
0.9 & 1 & 0.7 \\
0.7 & 0.7 & 1
\end{pmatrix},
\]
left-censored at 1.5

\[
P\{ Y(z) = 1 \mid S(0) = s_0, S(1) = s_1 \} =
= \Phi\{ \beta_0 + \beta_1 z + \beta_2 (1 - z) s_0 + \beta_3 z s_1 \}, \quad z = 0, 1
\]

\[
\text{TE}(s_1) := \text{mCEP}(s_1) \text{ defined by } h(x, y) = 1 - x/y
\]
Simulation setup

Three estimators for $\text{TE}(s_1)$:

1. **NP-TE**: nonparametric generalized-product kernel density estimation of Hall, Racine, and Li (2004); bandwidths optimized by likelihood cross-validation

2. **MLE-TE**: Gaussian maximum likelihood density estimation

3. **PSN**: pseudo-score estimation of Huang (2017) assuming
   
   $$P\{Y(z) = 1|S(1) = s_1\} = \Phi\{\gamma_0 + \gamma_1 z + \gamma_2 s_1 + \gamma_3 s_1 z\},$$
   
   $z = 0, 1$
Relative bias of $\hat{\text{TE}}(s_1)$

Results based on $10^3$ replicated data sets
Mean squared error of $\hat{\text{TE}}(s_1)$

Results based on $10^3$ replicated data sets
Coverage probabilities of pointwise 95% CIs for $\text{TE}(s_1)$

Results based on $10^3$ replicated data sets with 500 bootstrap samples drawn in each data set
Coverage probabilities of simultaneous 95% CI for \( \{ \text{TE}(s_1), s_1 \in S \} \)

<table>
<thead>
<tr>
<th>( \pi )</th>
<th>NP-TE</th>
<th>MLE-TE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.959</td>
<td>0.943</td>
</tr>
<tr>
<td>0.25</td>
<td>0.956</td>
<td>0.944</td>
</tr>
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<td>0.5</td>
<td>0.959</td>
<td>0.954</td>
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</tbody>
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Results based on \( 10^3 \) replicated data sets with 500 bootstrap samples drawn in each data set.
Size/power of hypothesis tests

<table>
<thead>
<tr>
<th>$\pi$</th>
<th>Test of $H_0^1$</th>
<th>Test of $H_0^2$</th>
<th>Test of $H_0^4$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Size</td>
<td>Power</td>
<td>Size</td>
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<tr>
<td>NP-TE</td>
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<td></td>
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</tr>
<tr>
<td>0.1</td>
<td>0.01</td>
<td>0.73</td>
<td>0.04</td>
</tr>
<tr>
<td>0.25</td>
<td>0.01</td>
<td>0.84</td>
<td>0.05</td>
</tr>
<tr>
<td>0.5</td>
<td>0.01</td>
<td>0.89</td>
<td>0.05</td>
</tr>
<tr>
<td>MLE-TE</td>
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</tr>
<tr>
<td>0.1</td>
<td>0.01</td>
<td>0.87</td>
<td>0.06</td>
</tr>
<tr>
<td>0.25</td>
<td>0.01</td>
<td>0.91</td>
<td>0.05</td>
</tr>
<tr>
<td>0.5</td>
<td>0.01</td>
<td>0.92</td>
<td>0.06</td>
</tr>
</tbody>
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$H_0^1 : TE(s_1) \equiv TE$ for all $s_1 \in S$

$H_0^2 : TE(s_1) \equiv 0.5$ for all $s_1 \in S$

$H_0^4 : TE(s_1|X = 1) = TE(s_1|X = 0)$ for all $s_1 \in S$

Results based on $10^3$ replicated data sets with 500 bootstrap samples drawn in each data set
Analysis of CYD14/CYD15 Dengvaxia trials

- Current age indication ≥ 9 years
- Trial-pooled analysis in 24,768 children aged ≥ 9 years at risk for VCD at month 13
- \( S = \text{average of } \log_{10} \text{ neutralizing antibody titers to 4 dengue vaccine strains at month 13} \)

<table>
<thead>
<tr>
<th>Controls ((Y = 0))</th>
<th>Cases ((Y = 1))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S)</td>
<td>2766</td>
</tr>
<tr>
<td>(S_b)</td>
<td>2759</td>
</tr>
</tbody>
</table>

- Goal: to assess modification of Dengvaxia’s effect on VCD risk through month 25 by \( S(1) \)
Two mCEP\((s_1)\) estimands:

1. \(h_1(x, y) = \log(x/y)\)
2. \(h_2(x, y) = y - x\)

1. **NP**: estimate \(P\{Y(z) = 1\mid X, S(z)\}\), \(z = 0, 1\), via IPW logistic regression models
   - \(X\) = age category (\(\leq 11\) vs. \(> 11\) years) and country
   - Hinge model (Fong et al., 2017) for modeling the effect of \(S(z)\) using the `chngptm` function in the R `chngpt` package

2. **PSN** (Huang, 2017): estimate \(P\{Y(z) = 1\mid X, S(1)\}\), \(z = 0, 1\), via IPW probit models with the same \(X\) and hinge model
Analysis of CYD14/CYD15 Dengvaxia trials

Proposed NP Estimator

PSN Estimator

Month 13 Average Titer of Vaccinees

Log Relative Risk

Vaccine Efficacy (%)

Hinge Point = 57

H_0^1: p < 0.001

H_0^2: p < 0.001

Month 13 Average Titer of Vaccinees

Log Relative Risk

Vaccine Efficacy (%)

Hinge Point = 94

H_0^1: p = 0.16

H_0^2: p < 0.001

Month 13 Average Titer of Vaccinees

Risk Difference (Placebo – Vaccine)

Risk Difference (Placebo – Vaccine)
R package \texttt{pssmooth} on CRAN

![Graph 1](https://cran.r-project.org/package=pssmooth)

Month 13 Average Titer of Vaccinees

Log Relative Risk

Vaccine Efficacy (%)

Proposed NP Estimator

Pointwise 95\% CI

Simultaneous 95\% CI

Hinge Point = 57

\(H_0^1: p < 0.001\)

\(H_0^2: p < 0.001\)

Risk Difference (Placebo – Vaccine)

\(H_0^1: p = 0.16\)

\(H_0^2: p < 0.001\)
Summary

The proposed methods:

- Provide an alternative to PS estimation methods\(^1\), which do not assume:
  - \( P\{ Y(0) = 1 \mid X, S(0) \} \) follows a GLM
  - PS methods instead assume \( P\{ Y(0) = 1 \mid X, S(1) \} \) follows a GLM
  - \( Y(0) \perp \perp S(1) \mid X, S(0) \)
  - \( S(1) \mid X, S(0) \overset{d}{=} S(1) \mid X, S_b \)
- Allow flexible nonparametric kernel smoothing
- Provide formal tests of
  - \( H_0^2 : m\text{CEP}(s_1) \equiv c \)
  - \( H_0^3 : m\text{CEP}_1(s_1) = m\text{CEP}_2(s_1) \)
  - \( H_0^4 : m\text{CEP}(s_1 \mid X = 1) = m\text{CEP}(s_1 \mid X = 0) \)

\(^1\) Huang, Gilbert, and Wolfson (2013); Huang (2017)


Extra Slides
Distributions of $S(0)$ and $S(1)$

**CYD14**

- Placebo Cases
- Placebo Controls
- Vaccine Cases
- Vaccine Controls

**CYD15**

- Placebo Cases
- Placebo Controls
- Vaccine Cases
- Vaccine Controls

Month 13 Average NAb titer

LLOQ

$10^0$ $10^1$ $10^2$ $10^3$ $10^4$ $10^5$
Acknowledgements

Fred Hutchinson Cancer Research Center
Peter B. Gilbert    Ying Huang    Ted Holzman
Youyi Fong       Zoe Moodie        Yingying Zhuang

CYD14/CYD15 study participants and investigators

Sanofi Pasteur
Sponsored and conducted the trials
Generated immunological and virological data for correlates analyses
Provided grant funding to Fred Hutch biostatistics for correlates study design and analyses

The Journal of Infectious Diseases

Neutralizing Antibody Correlates Analysis of Tetravalent Dengue Vaccine Efficacy Trials in Asia and Latin America

Zoe Moodie,1 Michal Juraska,1 Ying Huang,1,2 Yingying Zhuang,2 Youyi Fong,2,12 Lindsay N. Carpp,1 Steven G. Self,1,12 Laurent Chambonneau,3
Robert Small,4 Nicholas Jackson,5 Fernando Noriega,4 and Peter B. Gilbert1,12

1Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington; 2Department of Biostatistics, University of Washington, Seattle; 3Sanofi Pasteur, Marcy-L’Etoile, France; 4Sanofi Pasteur, Swiftwater, Pennsylvania; 5Sanofi Pasteur, Lyon, France