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

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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: $\widehat{VE} = 56.5\%$ (95% CI, 43.8 to 66.4)
- Latin American trial: $\widehat{VE} = 60.8\%$ (95% CI, 52.0 to 68.0)

Does average neutralizing antibody titer, measured in the vaccine group at month 13, modify 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 $\mathcal{S}$) 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 $\mathcal{S}$ and in all post-month 13 VCD cases
- Phase 3: biomarker's baseline value S_b only in a subset of subcohort $\mathcal{S}$

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!

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

To evaluate $S(1)$ as a modifier of treatment effect on Y,
S needs to be measured prior to Y.
$\Rightarrow$ Analysis restricted to participants with $Y^\tau = 0$.

Three-phase case-cohort sampling design

Phase 1: Z, $\boldsymbol{X}$, Y^τ, Y measured in all randomized participants

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

- Bernoulli sample $\mathcal{S}$ at baseline
- S measured at τ in
  - a subset of $\mathcal{S}$ 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 $\mathcal{S}$ with $Y^\tau = 0$

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

Identifiability assumptions

1. $(Z_i, \boldsymbol{X}_i, \delta_i, \delta_i S_{b,i}, Y_i^\tau(0), Y_i^\tau(1), \epsilon_i(0), \epsilon_i(0)S_i(0), \epsilon_i(1), \epsilon_i(1)S_i(1), Y_i(0), Y_i(1))$, $i = 1, \ldots, n$, i.i.d. with no drop-out
2. Standard identifiability assumptions†
   a. Stable unit treatment value assumption (SUTVA) and consistency:
   $(Y_i^\tau(0), Y_i^\tau(1), \epsilon_i(0), \epsilon_i(0)S_i(0), \epsilon_i(1), \epsilon_i(1)S_i(1), Y_i(0), Y_i(1)) \perp\!\!\!\perp Z_j$, $j \neq i$, 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:
   $Z_i \perp\!\!\!\perp (\delta_i, \delta_i S_{b,i}, Y_i^\tau(0), Y_i^\tau(1), \epsilon_i(0), \epsilon_i(0)S_i(0), \epsilon_i(1), \epsilon_i(1)S_i(1), Y_i(0), Y_i(1)) \mid \boldsymbol{X}_i$
   c. Equal early clinical risk:
   $P\{Y_i^\tau(0) = Y_i^\tau(1)\} = 1$*

* Henceforth all unconditional and conditional probabilities of $Y(z) = 1$ implicitly condition on $Y^\tau(1) = Y^\tau(0) = 0$.

† Gilbert and Hudgens (2008); Huang and Gilbert (2011); Huang, Gilbert, and Wolfson (2013); Gabriel and Gilbert (2014); Huang (2017)

Modeling assumptions

3. $P\{Y(z) = 1|\boldsymbol{X}, S(z)\}$ follows a GLM for $z = 0, 1$
   - For $z = 0$, it replaces "placebo structural risk" assumption of all EML and PS methods† that $P\{Y(0) = 1|\boldsymbol{X}, S(1)\}$ follows a GLM
4. Conditional independence:
   $P\{Y(0) = 1|\boldsymbol{X}, S(0), S(1)\} = P\{Y(0) = 1|\boldsymbol{X}, S(0)\}$
5. Time constancy:
   $f(s_1|\boldsymbol{X} = \boldsymbol{x}, S(0) = s_0) = \widetilde{f}(s_1|\boldsymbol{X} = \boldsymbol{x}, S_b = s_0)$ for all $(s_1, \boldsymbol{x}, s_0)$

† Gilbert and Hudgens (2008); Huang and Gilbert (2011); Huang, Gilbert, and Wolfson (2013); Gabriel and Gilbert (2014); Huang (2017)

Estimand of interest: $\mathrm{mCEP}(s_1)$

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

[*] Gilbert and Hudgens (2008)
[†] If S is continuous, this definition abuses notation for simplicity of exposition.
[‡] Frangakis and Rubin (2002)

Estimation of $\mathrm{mCEP}(s_1)$

- $p_z(s_1) := P\{Y(z) = 1 | S(1) = s_1\}$ for $z = 0, 1$
- $\mathrm{mCEP}(s_1) = h\{p_1(s_1), p_0(s_1)\}$
- Estimate $p_1(s_1)$ via the specified GLM, accounting for case-cohort sampling of S
  - E.g., using the `tps` function in the R `osDesign` package

Estimation of mCEP(s_1)

$$p_0(s_1) = \int P\{Y(0) = 1 | \boldsymbol{X} = \boldsymbol{x}, S(0) = s_0\} \times \\ \times \frac{f(s_1 | s_0, \boldsymbol{x}) g(s_0 | \boldsymbol{x}) r(\boldsymbol{x})}{m(s_1)} \, \mathrm{d}^{k+1}(s_0, \boldsymbol{x}),$$

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

- Estimate $P\{Y(0) = 1 | \boldsymbol{X} = \boldsymbol{x}, S(0) = s_0\}$ via the specified GLM, accounting for case-cohort sampling of S
- Estimate $f(s_1 | S_0 = s_0, \boldsymbol{X} = \boldsymbol{x})$ by estimating $\widetilde{f}(s_1 | S_b = s_0, \boldsymbol{X} = \boldsymbol{x})$ 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 $g(s_0 | \boldsymbol{x})$ and $r(\boldsymbol{x})$ analogously

Interval estimation of $\mathrm{mCEP}(s_1)$

Bootstrap procedures designed to construct

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

- Cases and controls sampled separately in each bootstrap sample

Simultaneous Wald-type CI for $\{\mathrm{mCEP}(s_1), s_1 \in \mathbb{S}\}$

- $\eta(s_1) := \eta\{\mathrm{mCEP}(s_1)\}$ a "symmetrizing" transformation
  - $h(x, y) = 1 - x/y \;\Rightarrow\; \eta\{h(x, y)\} = \log\{1 - h(x, y)\}$
- $\widehat{\eta}(s_1) = \eta\{\widehat{\mathrm{mCEP}}(s_1)\}$
- $U^{(b)} := \sup_{s_1 \in \mathbb{S}} \left|\widehat{\eta}^{(b)}(s_1) - \widehat{\eta}(s_1)\right| / SE^*\{\widehat{\eta}(s_1)\}$
- c^*_α empirical quantile of $U^{(b)}$, $b = 1, \ldots, B$, at probability $1 - \alpha$
- $(1 - \alpha) \times 100\%$ CI as $\eta^{-1}(\cdot)$ transformation of

$$(l^\eta_\alpha(s_1), u^\eta_\alpha(s_1)) = \widehat{\eta}(s_1) \mp c^*_\alpha \, SE^*\{\widehat{\eta}(s_1)\}.$$

Testing hypotheses of interest

Hypothesis tests via simultaneous estimation method of Roy and Bose (1953) for

1. $H_0^1 : \mathrm{mCEP}(s_1) \equiv CE$ for all $s_1 \in \mathbb{S}$
2. $H_0^2 : \mathrm{mCEP}(s_1) \equiv c$ for all $s_1 \in \mathbb{S}_1 \subseteq \mathbb{S}$ and a known constant $c \in \mathbb{R}$
3. $H_0^3 : \mathrm{mCEP}_1(s_1) = \mathrm{mCEP}_2(s_1)$ for all $s_1 \in \mathbb{S}_1 \subseteq \mathbb{S}$, where mCEP_1 and mCEP_2 are each associated with either a different biomarker (measured in the same units) or a different endpoint or both
4. $H_0^4 : \mathrm{mCEP}(s_1|X = 1) = \mathrm{mCEP}(s_1|X = 0)$ for all $s_1 \in \mathbb{S}_1 \subseteq \mathbb{S}$, where X is a baseline dichotomous phase 1 covariate of interest included in $\boldsymbol{X}$

Tests of H_0^1 and H_0^2

$H_0^1 : \mathrm{mCEP}(s_1) \equiv CE$ for all $s_1 \in \mathbb{S}$
$H_0^2 : \mathrm{mCEP}(s_1) \equiv c$ for all $s_1 \in \mathbb{S}_1 \subseteq \mathbb{S}$ and a known constant $c \in \mathbb{R}$

- $U_\eta^{(b)}(\mathbb{S}, a) := \sup_{s_1 \in \mathbb{S}} \left|\widehat{\eta}^{(b)}(s_1) - \eta(a)\right| / SE^*\{\widehat{\eta}(s_1)\}$, $a \in \mathbb{R}$
- Regions of rejection of H_0^1 and H_0^2 at significance level α:

$$U_1 := \sup_{s_1 \in \mathbb{S}} \left|\widehat{\eta}(s_1) - \eta(\widehat{CE})\right| / SE^*\{\widehat{\eta}(s_1)\} > c_{1\alpha}^*$$

$$U_2 := \sup_{s_1 \in \mathbb{S}_1} \left|\widehat{\eta}(s_1) - \eta(c)\right| / SE^*\{\widehat{\eta}(s_1)\} > c_{2\alpha}^*$$

- $c_{1\alpha}^*$ and $c_{2\alpha}^*$ empirical quantiles of $U_\eta^{(b)}(\mathbb{S}, \widehat{CE})$ and $U_\eta^{(b)}(\mathbb{S}_1, c)$, $b = 1, \ldots, B$, at probability $1 - \alpha$
- Two-sided p-values as empirical probabilities that $U_\eta^{(b)}(\mathbb{S}, \widehat{CE}) > U_1$ and $U_\eta^{(b)}(\mathbb{S}_1, c) > U_2$

Test of H_0^3

$H_0^3 : \mathrm{mCEP}_1(s_1) = \mathrm{mCEP}_2(s_1)$ for all $s_1 \in \mathbb{S}_1 \subseteq \mathbb{S}$, where mCEP_1 and mCEP_2 are each associated with either a different biomarker or a different endpoint or both

- $\theta(s_1) := \eta\{\mathrm{mCEP}_1(s_1)\} - \eta\{\mathrm{mCEP}_2(s_1)\}$
- $U_\theta^{(b)} := \sup_{s_1 \in \mathbb{S}_1} \left|\widehat{\theta}^{(b)}(s_1)\right| / SE^*\{\widehat{\theta}(s_1)\}$
- Region of rejection of H_0^3 at significance level α:

$$U_3 := \sup_{s_1 \in \mathbb{S}_1} \left|\widehat{\theta}(s_1)\right| / SE^*\{\widehat{\theta}(s_1)\} > c_{3\alpha}^*$$

- $c_{3\alpha}^*$ 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

$H_0^4 : \mathrm{mCEP}(s_1|X=1) = \mathrm{mCEP}(s_1|X=0)$ for all $s_1 \in \mathbb{S}_1 \subseteq \mathbb{S}$, where X is a baseline dichotomous phase 1 covariate of interest

- Estimates of $\mathrm{mCEP}(s_1)$ in subgroups $X=1$ and $X=0$ are independent
- Test of H_0^4 identical to that of H_0^3 except

$$SE^*\{\widehat{\theta}(s_1)\} = \Big\{ SE^{*^2}\left[\eta\{\widehat{\mathrm{mCEP}}(s_1|X=1)\}\right] + \\ + SE^{*^2}\left[\eta\{\widehat{\mathrm{mCEP}}(s_1|X=0)\}\right] \Big\}^{1/2}$$

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 τ at which $S(Z)$ is measured)

Phase 2:

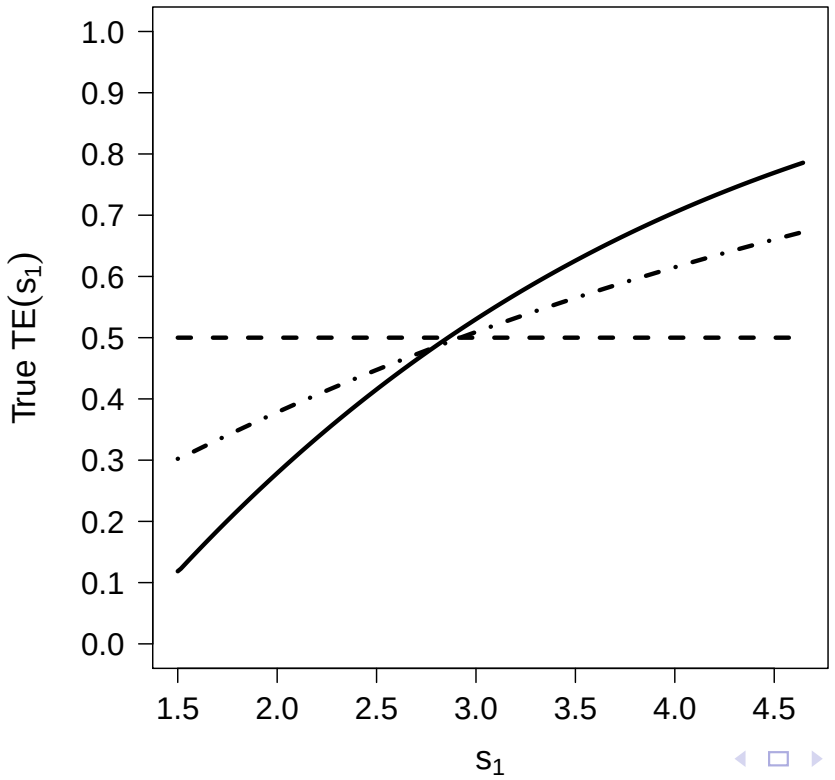
- Bernoulli sample $\mathcal{S}$ at baseline with sampling probability $\pi = 0.1$, 0.25, and 0.5
- $S(Z)$ measured at τ in $\mathcal{S}$ and in all cases ($Y = 1$)

Phase 3:

- S_b measured at baseline in $\mathcal{S}$ only, i.e., S_b missing in cases not included in $\mathcal{S}$

Simulation setup

- $\begin{pmatrix} S_b \\ S(0) \\ S(1) \end{pmatrix} \sim \mathrm{N}\left(\begin{pmatrix} 2 \\ 2 \\ 3 \end{pmatrix}, \begin{pmatrix} 1 & 0.9 & 0.7 \\ 0.9 & 1 & 0.7 \\ 0.7 & 0.7 & 1 \end{pmatrix} \right)$, left-censored at 1.5
- $P\{Y(z) = 1 | S(0) = s_0, S(1) = s_1\} = \\ = \Phi\{\beta_0 + \beta_1 z + \beta_2(1-z)s_0 + \beta_3 z s_1\}, \quad z = 0, 1$
- $\mathrm{TE}(s_1) := \mathrm{mCEP}(s_1)$ defined by $h(x, y) = 1 - x/y$

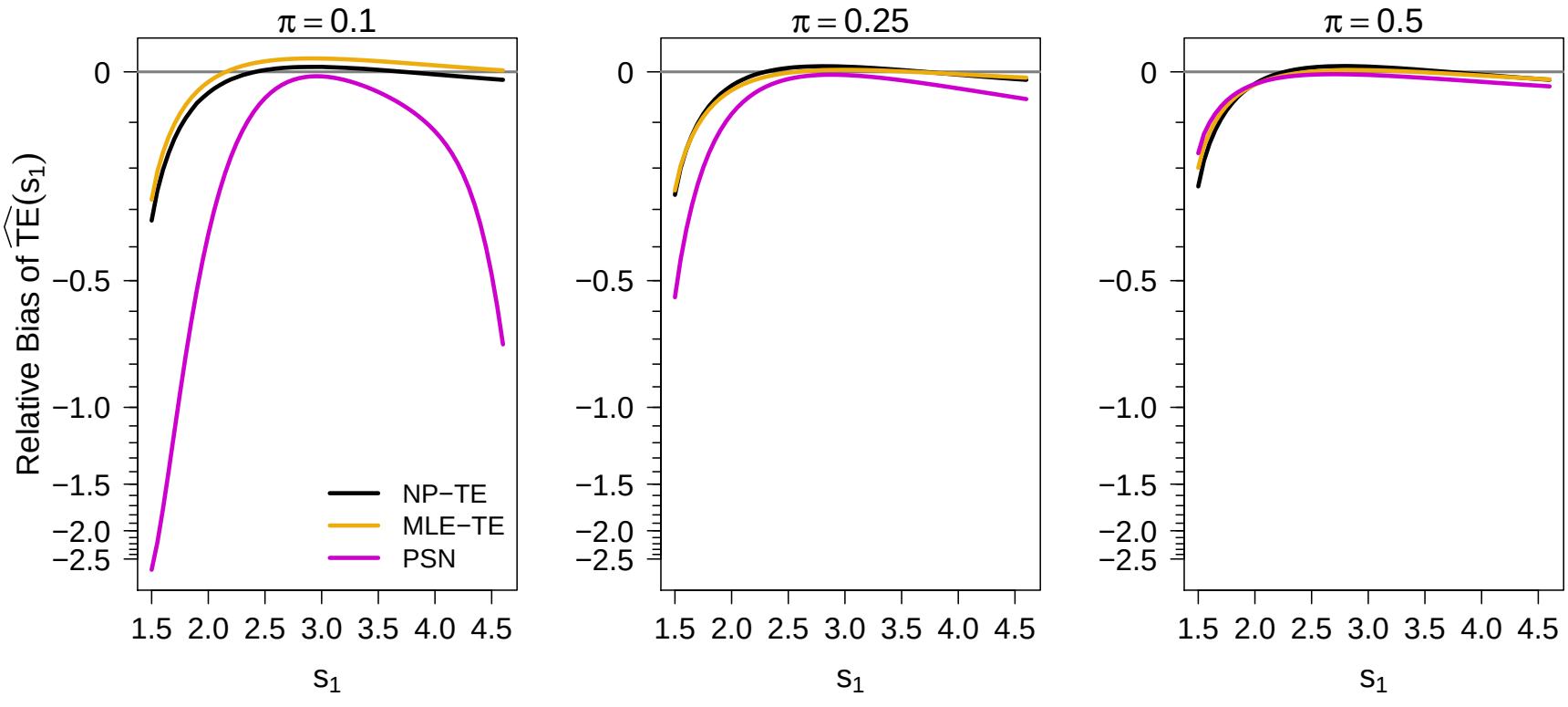


Simulation setup

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

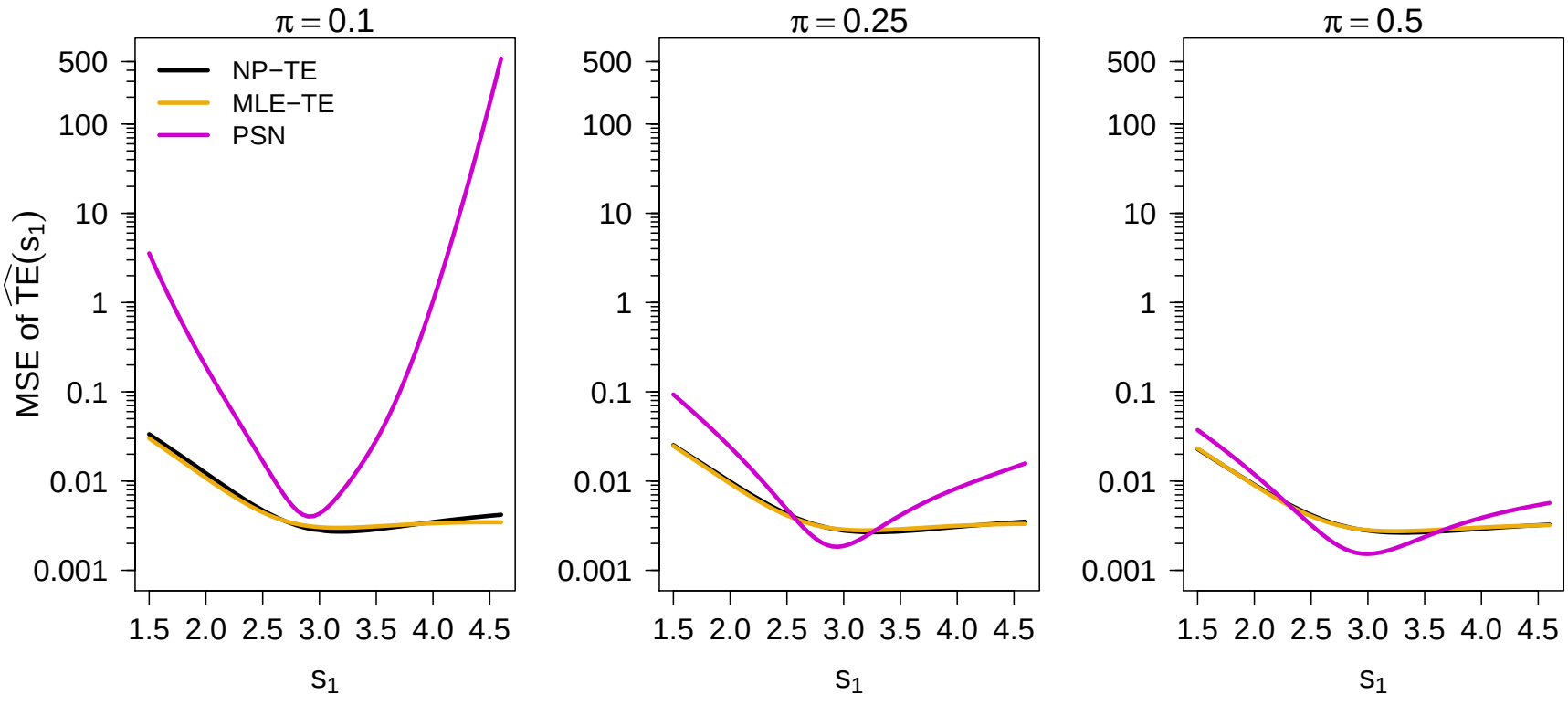
1. NP-TE: nonparametric generalized-product kernel density estimation of Hall, Racine, and Li (2004); bandwidths optimized by likelihood cross-validation
2. MLE-TE: Gaussian maximum likelihood density estimation
3. PSN: pseudo-score estimation of Huang (2017) assuming $P\{Y(z) = 1 | S(1) = s_1\} = \Phi\{\gamma_0 + \gamma_1 z + \gamma_2 s_1 + \gamma_3 s_1 z\}$, $z = 0, 1$

Relative bias of $\widehat{\mathrm{TE}}(s_1)$



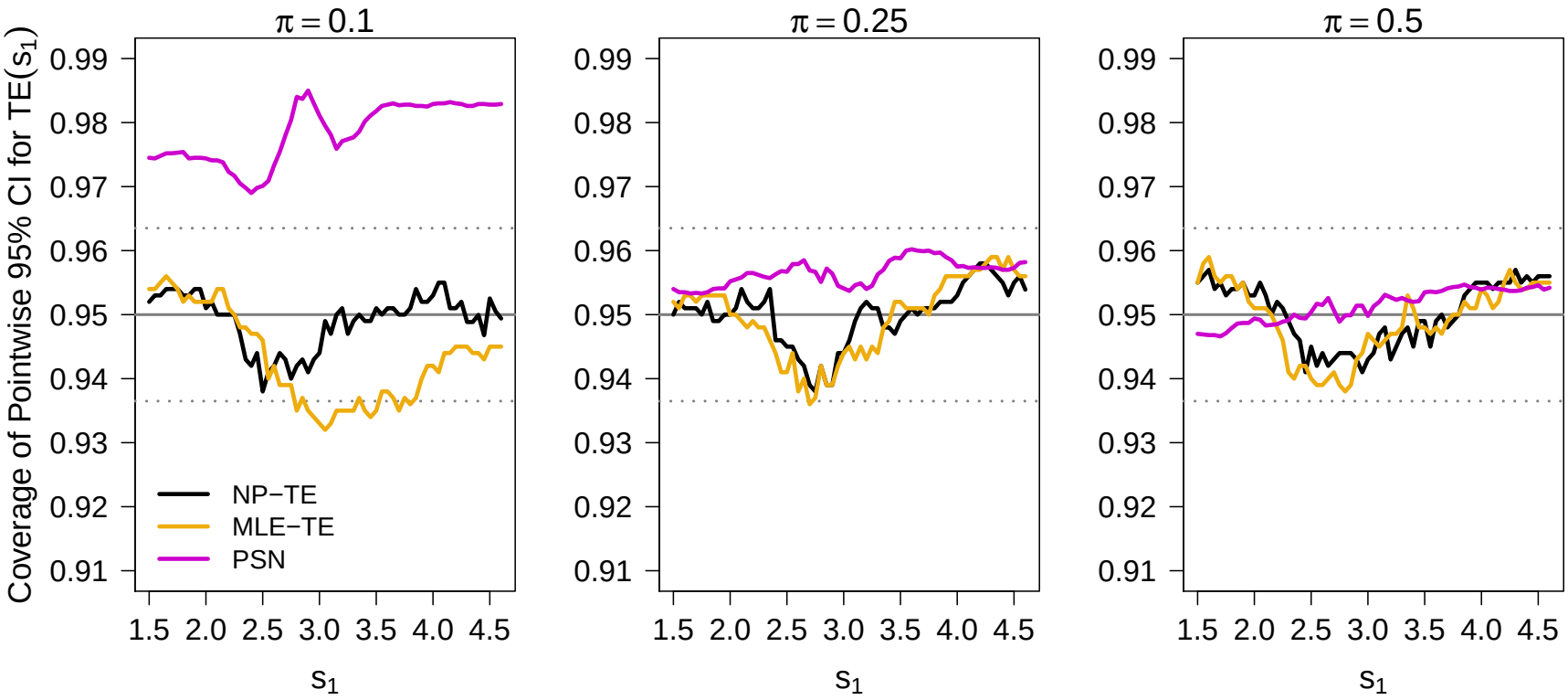
Results based on 10^3 replicated data sets

Mean squared error of $\widehat{\mathrm{TE}}(s_1)$



Results based on 10^3 replicated data sets

Coverage probabilities of pointwise 95% CIs for $\mathrm{TE}(s_1)$



Results based on 10^3 replicated data sets with 500 bootstrap samples drawn in each data set

Coverage probabilities of simultaneous 95% CI for $\{\mathrm{TE}(s_1), s_1 \in \mathbb{S}\}$

π	NP-TE	MLE-TE
0.1	0.959	0.943
0.25	0.956	0.944
0.5	0.959	0.954

Results based on 10^3 replicated data sets with 500 bootstrap samples drawn in each data set

Size/power of hypothesis tests

	Test of H_0^{1a}		Test of H_0^{2b}		Test of H_0^{4c}	
π	Size	Power	Size	Power	Size	Power
			NP-TE			
0.1	0.01	0.73	0.04	0.83	0.04	0.12
0.25	0.01	0.84	0.05	0.89	0.04	0.15
0.5	0.01	0.89	0.05	0.93	0.04	0.18
			MLE-TE			
0.1	0.01	0.87	0.06	0.92	0.05	0.17
0.25	0.01	0.91	0.05	0.95	0.05	0.20
0.5	0.01	0.92	0.06	0.96	0.05	0.20

[a] $H_0^1 : \mathrm{TE}(s_1) \equiv TE$ for all $s_1 \in \mathbb{S}$

[b] $H_0^2 : \mathrm{TE}(s_1) \equiv 0.5$ for all $s_1 \in \mathbb{S}$

[c] $H_0^4 : \mathrm{TE}(s_1|X = 1) = \mathrm{TE}(s_1|X = 0)$ for all $s_1 \in \mathbb{S}$

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
- $S =$ average of $\log_{10}$ neutralizing antibody titers to 4 dengue vaccine strains at month 13

	Controls ($Y = 0$)	Cases ($Y = 1$)
S	2766	502
S_b	2759	55

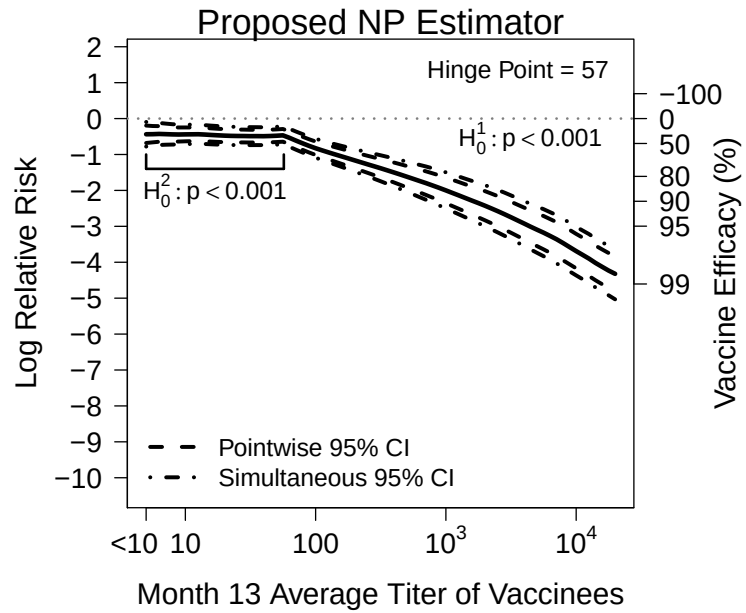
- Goal: to assess modification of Dengvaxia's effect on VCD risk through month 25 by $S(1)$

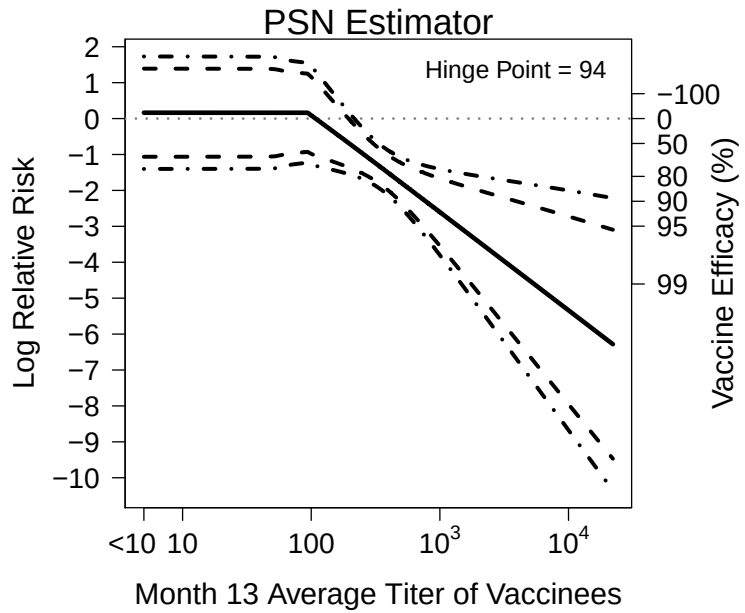
Analysis of CYD14/CYD15 Dengvaxia trials

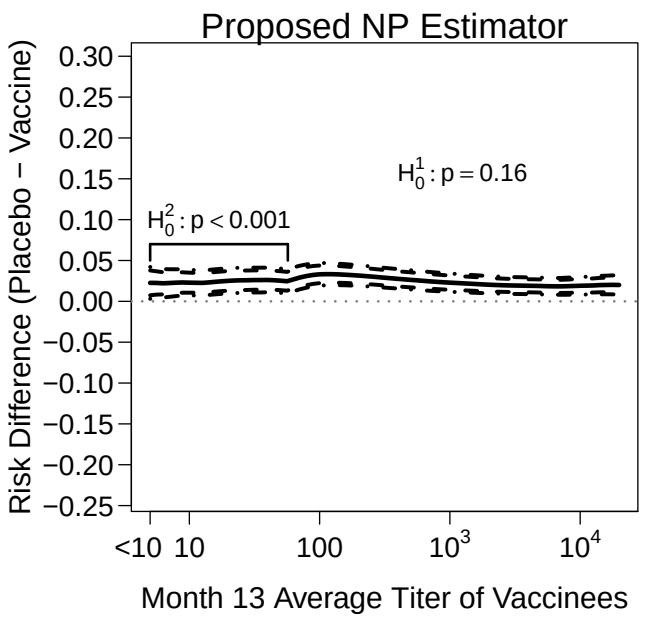
- Two $\mathrm{mCEP}(s_1)$ estimands:
  1. $h_1(x, y) = \log(x/y)$
  2. $h_2(x, y) = y - x$

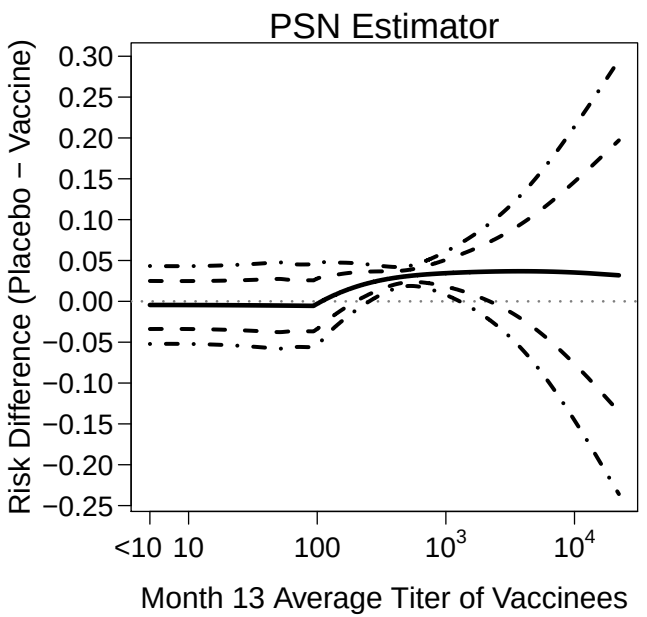
1. NP: estimate $P\{Y(z) = 1 | \boldsymbol{X}, S(z)\}$, $z = 0, 1$, via IPW logistic regression models
   - $\boldsymbol{X}$ = age category (≤ 11 vs. > 11 years) and country
   - Hinge model (Fong et al., 2017) for modeling the effect of $S(z)$ using the `chngptm` function in the R `chngpt` package
2. PSN (Huang, 2017): estimate $P\{Y(z) = 1 | \boldsymbol{X}, S(1)\}$, $z = 0, 1$, via IPW probit models with the same $\boldsymbol{X}$ and hinge model

Analysis of CYD14/CYD15 Dengvaxia trials

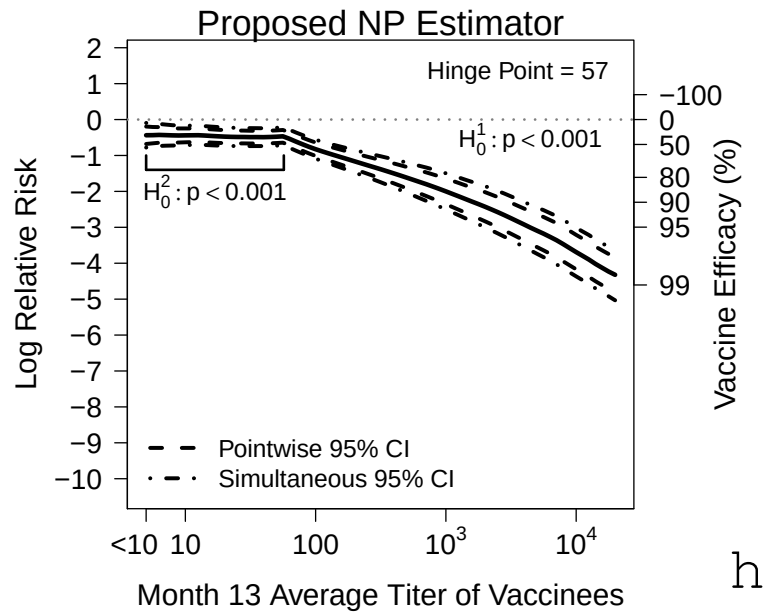


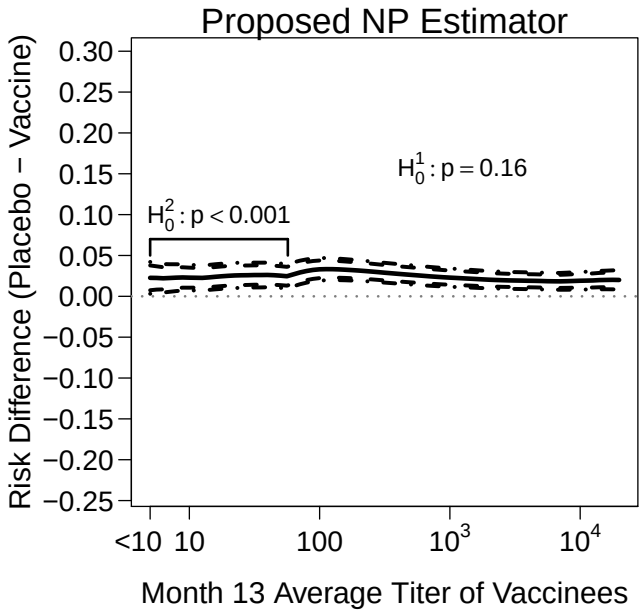






R package `pssmooth` on CRAN





`https://cran.r-project.org/package=pssmooth`

Summary

The proposed methods:

- Provide an alternative to PS estimation methods[1], which do **not** assume:
  - $P\{Y(0) = 1 \mid \boldsymbol{X}, S(0)\}$ follows a GLM
    - PS methods instead assume $P\{Y(0) = 1 \mid \boldsymbol{X}, S(1)\}$ follows a GLM
  - $Y(0) \perp\!\!\!\perp S(1) \mid \boldsymbol{X}, S(0)$
  - $S(1) \mid \boldsymbol{X}, S(0) \stackrel{d}{=} S(1) \mid \boldsymbol{X}, S_b$
- Allow flexible nonparametric kernel smoothing
- Provide formal tests of
  - $H_0^2 : \mathrm{mCEP}(s_1) \equiv c$
  - $H_0^3 : \mathrm{mCEP}_1(s_1) = \mathrm{mCEP}_2(s_1)$
  - $H_0^4 : \mathrm{mCEP}(s_1|X = 1) = \mathrm{mCEP}(s_1|X = 0)$

[1] Huang, Gilbert, and Wolfson (2013); Huang (2017)

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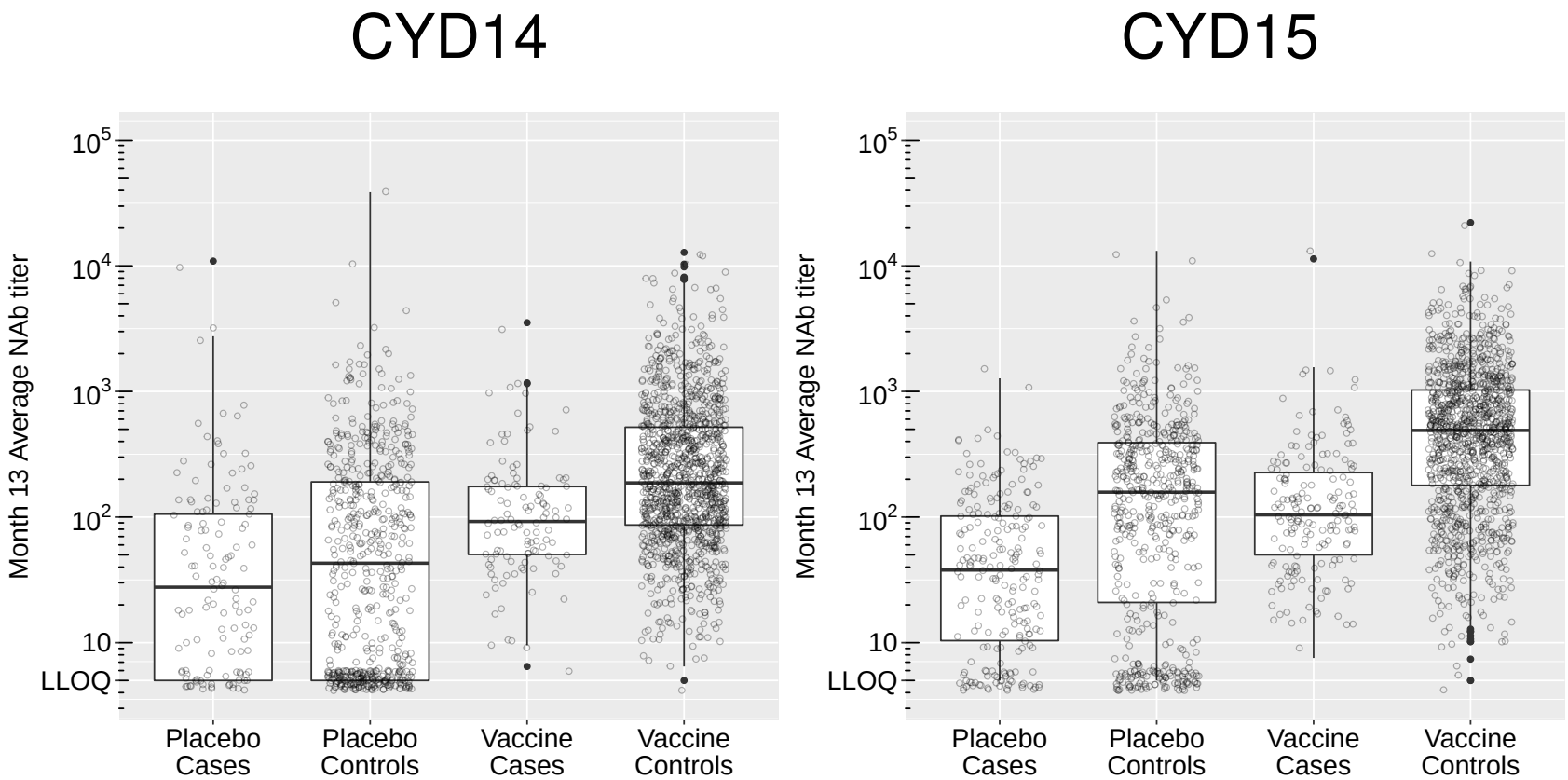
Extra Slides

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



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

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

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