Characterizing immune correlates of protection in vaccine efficacy trials with stochastic-interventional causal effects

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Joint work with P.B. Gilbert (Fred Hutch & UW)

Identifying immune correlates of vaccination for HIV-1 and COVID-19

The fights against HIV-1 and COVID-19

- The HIV-1 epidemic:
  - 1.5 million new infections occurring annually worldwide;
  - new infections outpace patients starting antiretroviral therapy;
  - HIV Vaccine Trials Network's (HVTN) *505* trial evaluated a novel antibody boost vaccine (Hammer et al. 2013).
- The COVID-19 ~~epi~~ ~~pan~~ endemic (Antia and Halloran 2021):
  - ~~270~~ ~~331~~ ~~619~~ ~~643~~ 770 million total cases detected globally;
  - new variants emerging, with continued formulation of targeted vaccines and annual roll-outs expected;
  - COVID-19 Prevention Network's (CoVPN) *COVE* trial focused on Moderna's (mRNA-1273) vaccine (Baden et al. 2021).

Evaluating vaccines for HIV-1 and COVID-19

- *505*: How would HIV-1 infection risk have differed had the boost vaccine modulated antibody responses differently?
- *COVE*: How would COVID-19 disease risk have differed for alternative vaccine-induced immunogenic response profiles?
- **Question**: How can [HIV-1, COVID-19] vaccines be improved through the modulation of immunogenic response profiles?

Why measure and analyze immune correlates?

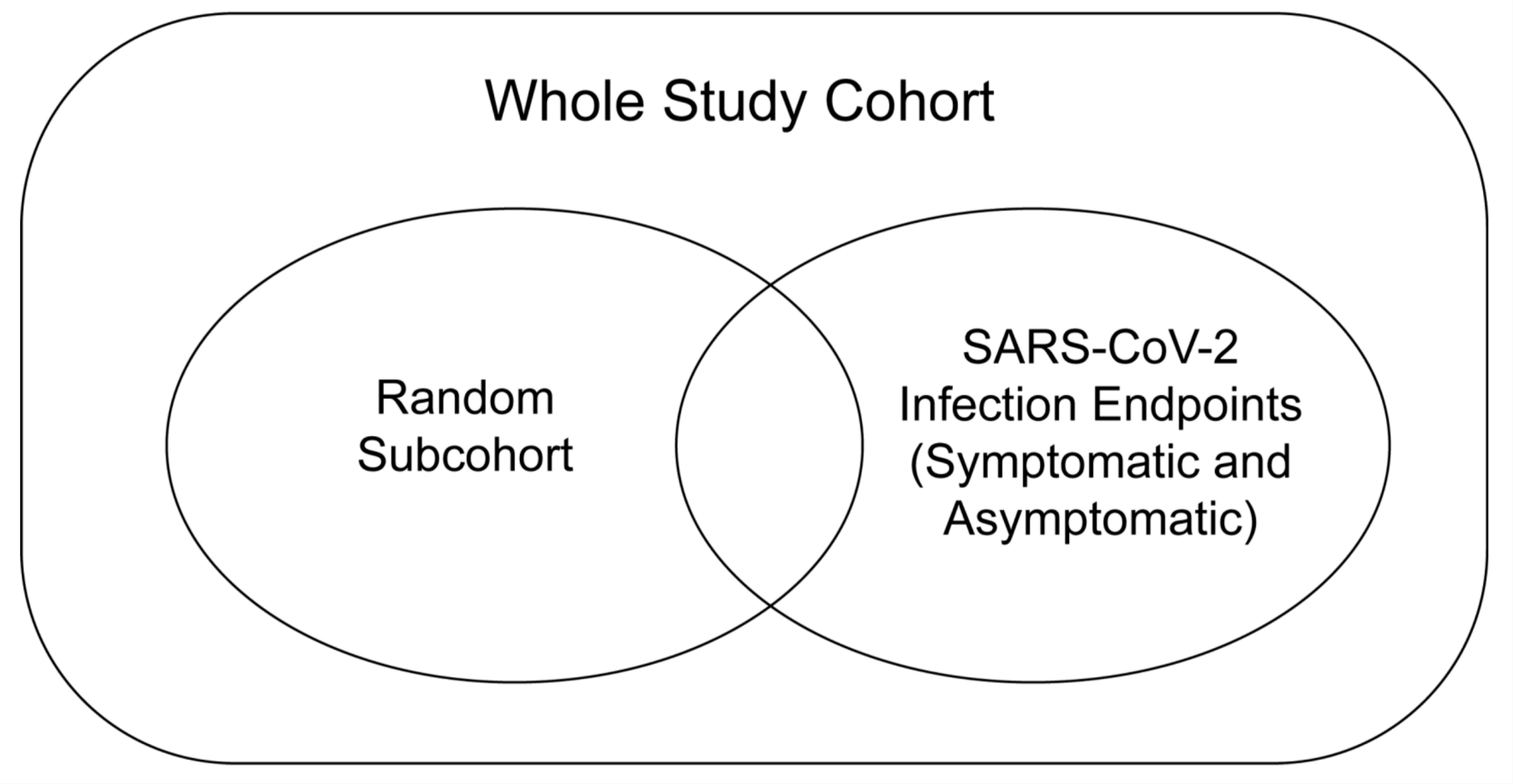
- Two, interrelated goals of immune correlates analyses are to
  - identify/validate possible *surrogate endpoints* (Prentice 1989);
  - understand/delineate *protective mechanisms* of vaccines.
- If an immune correlate is established to reliably predict VE, subsequent efficacy trials may use it as a primary endpoint.
- This may accelerate the approval of
  - existing vaccines in different populations (e.g., in children);
  - new vaccines within the same class (e.g., bivalent mRNA);
  - inform the development of "next-generation" vaccines.

Measuring correlates: Two-phase designs

- Often, use case-cohort design (Prentice 1986), a special case of two-phase sampling (Breslow et al. 2003).
- Phase 1: measure baseline, vaccination, endpoint on everyone.
- Phase 2: given baseline, vaccine, endpoint, select members of immune response subcohort with (possibly known) probability.
  - *505*: phase-two sample with 100% of HIV-1 cases and matching of non-cases ($n = 189$ per Janes et al. 2017).
  - *COVE*: stratified random subcohort ($n \approx 1600$) and all SARS-CoV-2 infection and COVID-19 disease endpoints.

A simple two-phase design: Case-cohort

Assaying >30k samples is expensive, statistically unnecessary.



Case-cohort design, per Prentice (1986), as applied to COVE.

Two-phase sampling masks the complete data structure

- Complete (unobserved) data $X = (L, A, S, Y) \sim P_0^X \in \mathcal{M}$:
  - L (baseline covariates): sex, age, BMI, behavioral HIV risk,
  - A (treatment): randomized assignment to vaccine/placebo,
  - S (exposure): immune response profile for relevant markers,
  - Y (outcome of interest): infection status at trial's end.
- Observed data $O = (V, B, BX) = (L, A, B, BS, Y) \sim P_0 \in \mathcal{M}$.
  - $V \equiv (L, Y)$ are used in defining *outcome-dependent* two-phase sampling mechanism $g_{0,B} := \mathbb{P}(B = 1 \mid V)$.
  - $B \in \{0, 1\}$ is an indicator of inclusion in the phase-two sample.
  - $g_{0,B} := \mathbb{P}(B = 1 \mid Y, L)$ must be *known by design* or estimated.

Causal effects for quantitative exposures

Static interventions aren't enough

- Describe the manner in which X is hypothetically generated by a nonparametric structural equation model (Pearl 2009):

  $$L = f_L(U_L); A \sim \text{Bern}(0.5); S = f_S(A, L, U_S); Y = f_Y(S, A, L, U_Y)$$

- Utility: Implies a model for the distribution of counterfactual RVs induced by interventions on the system under study.
- A *static* intervention replaces f_S with a specific value s in its conditional support, i.e., $S \mid L$.
- This requires specifying *a priori* a particular value of exposure under which to evaluate the outcome — but what value?

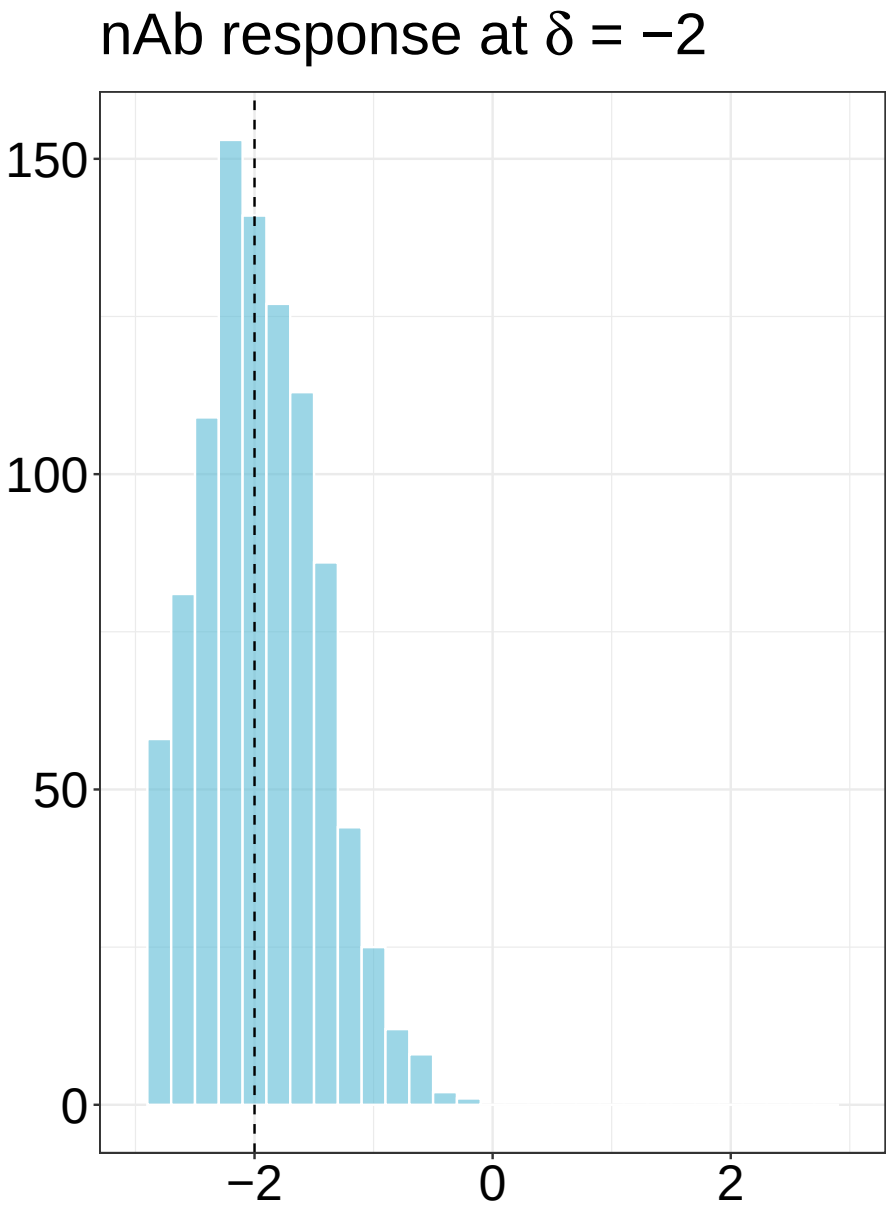
Controlled vaccine efficacy (CVE)

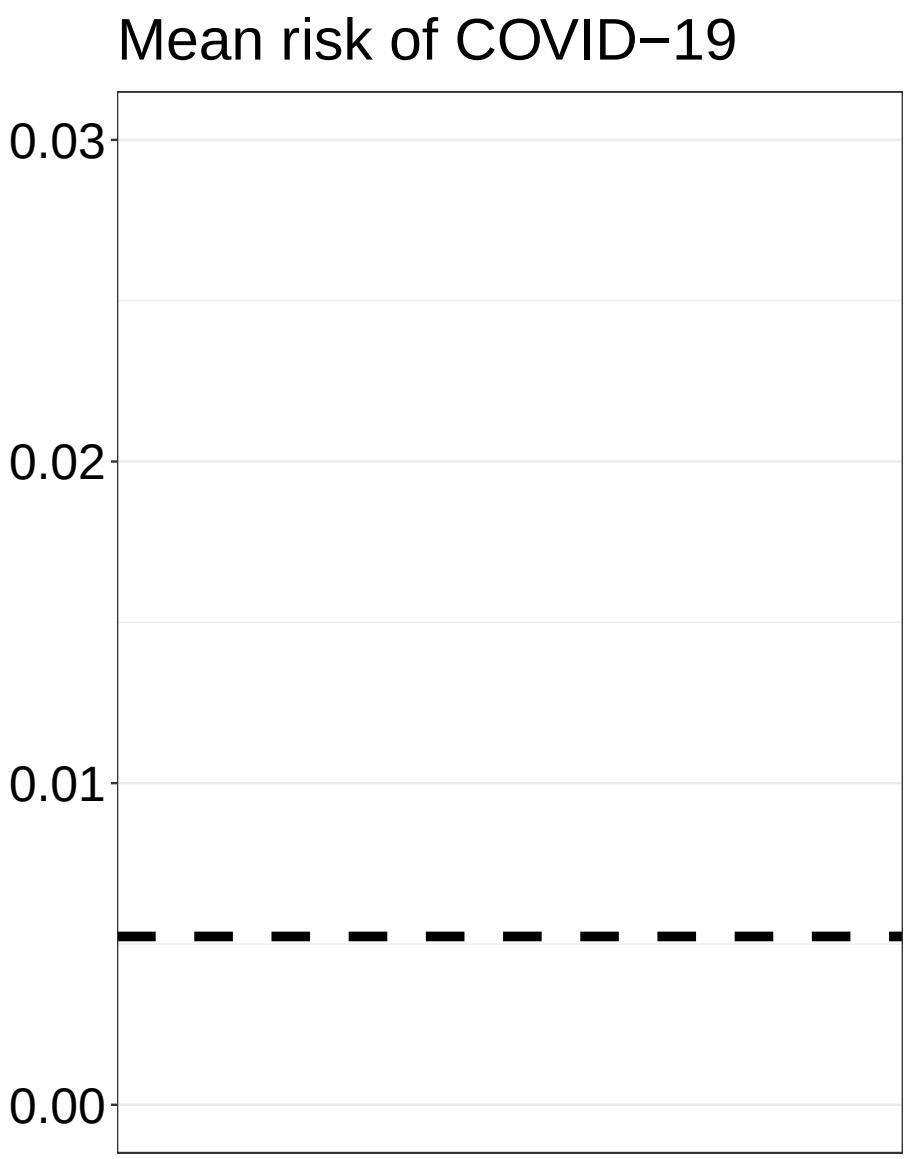
- For a hypothetical value $s \in \mathcal{S}$, the *controlled direct effect* (CDE) quantifies the effect of A on Y while fixing $S = s$.
- The hypothetical value $S = s$ must be chosen carefully — to be scientifically informative *and* to avoid positivity violations.
- For two hypothetical values $s_0, s_1 \in \mathcal{S}$, *Controlled Vaccine Efficacy* (CVE) (Gilbert et al. 2022) is

$$\text{CVE}(s_0, s_1) = 1 - \frac{\mathbb{E}[\mathbb{P}(Y = 1 \mid S = s_1, A = 1, L = l)]}{\mathbb{E}[\mathbb{P}(Y = 1 \mid \cancel{S = s_0}, A = 0, L = l)]},$$

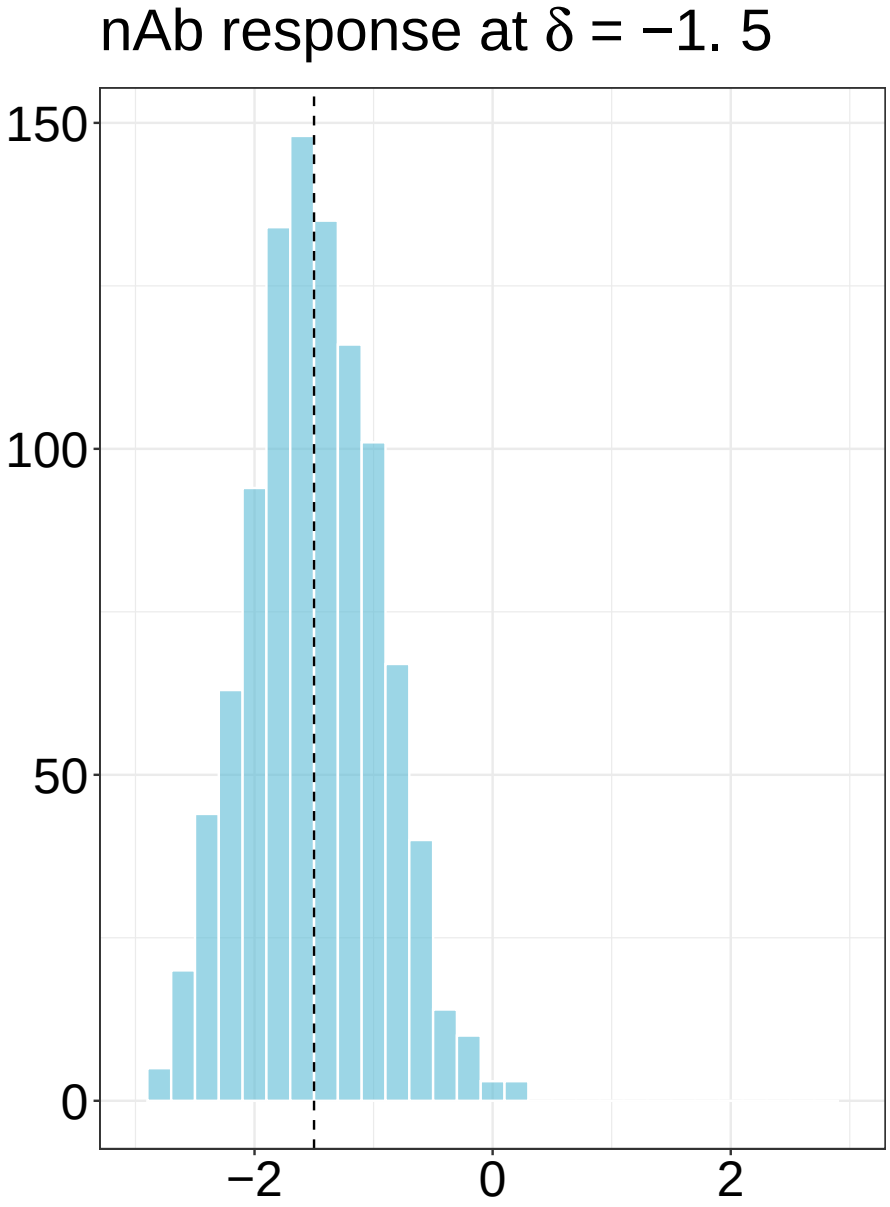
  which contrasts counterfactual risk for vaccine and $S = s_1$ vs. placebo and $S = s_0$, where $s_0 = 0$ by construction.

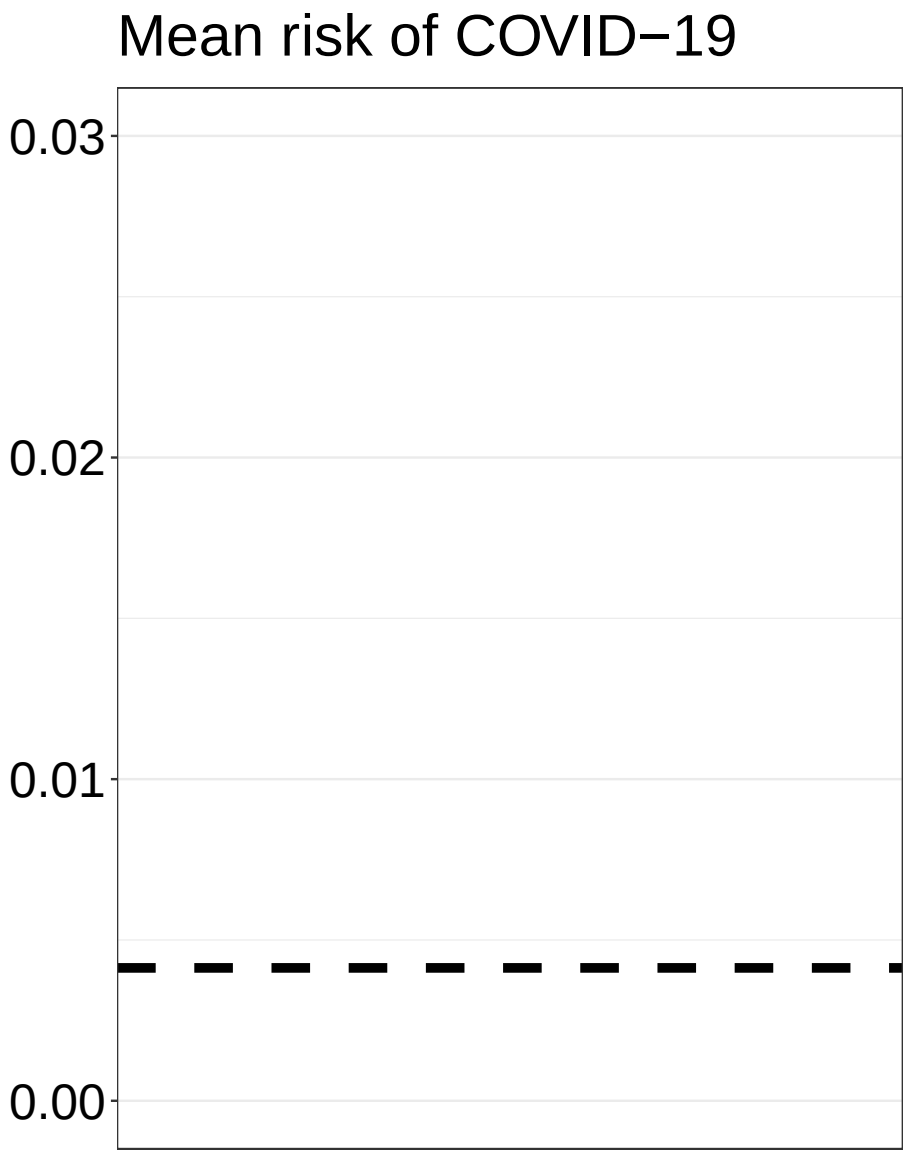
Disease risk under shifted immunogenic responses



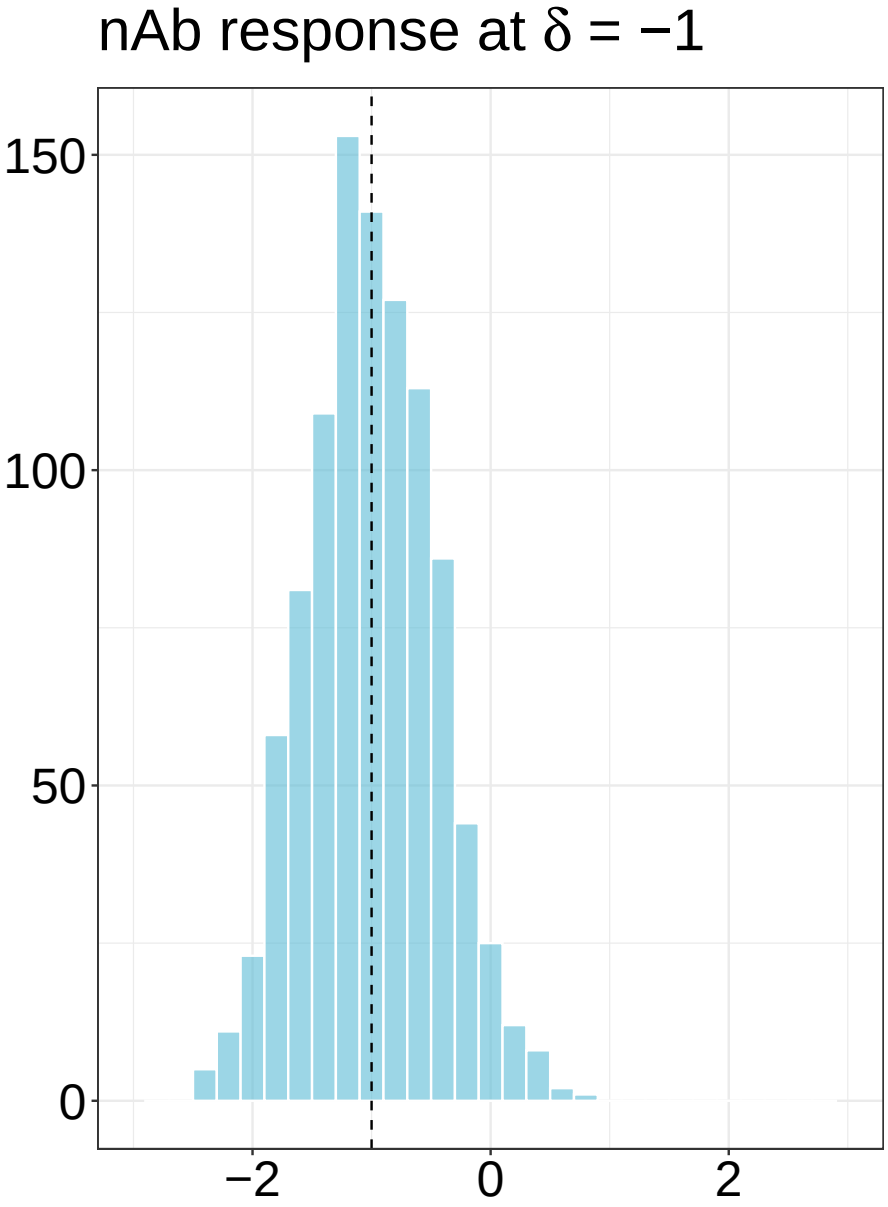


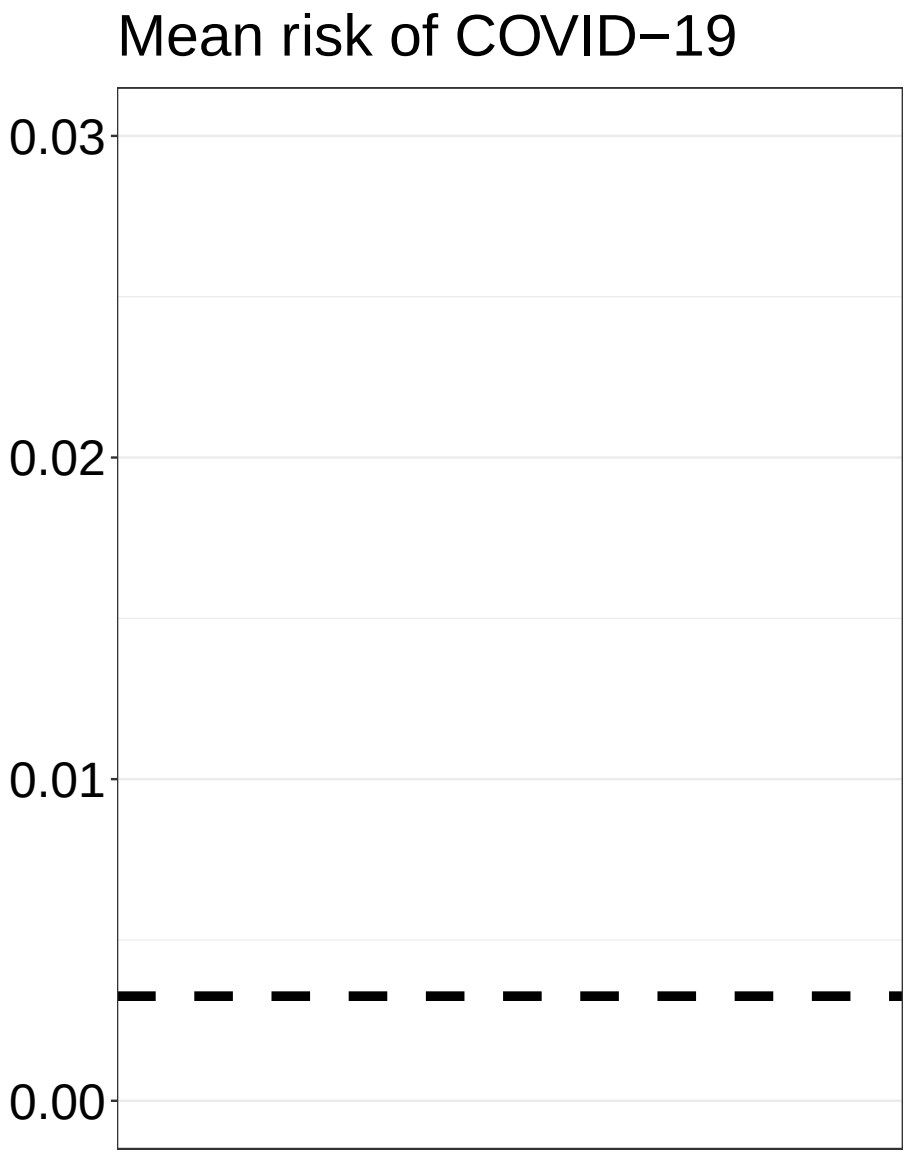
Disease risk under shifted immunogenic responses



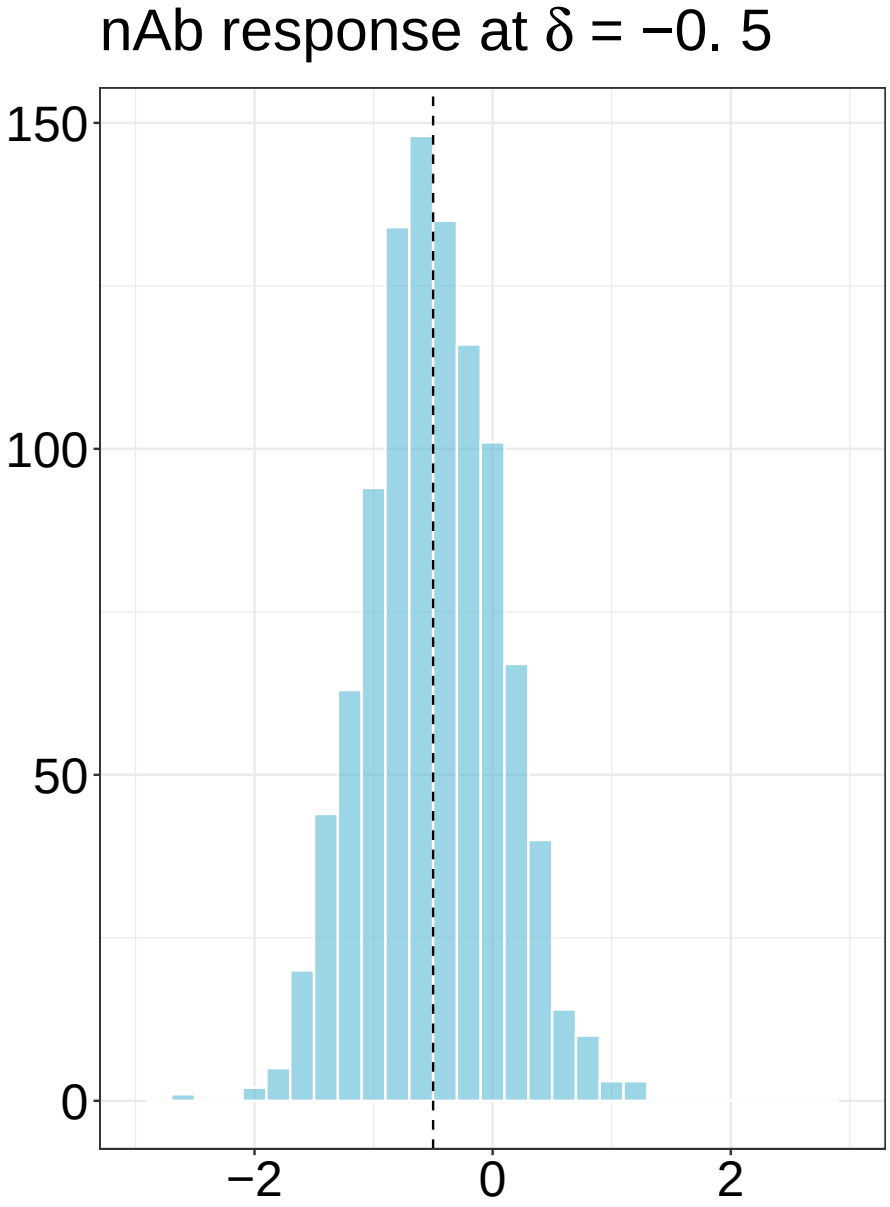


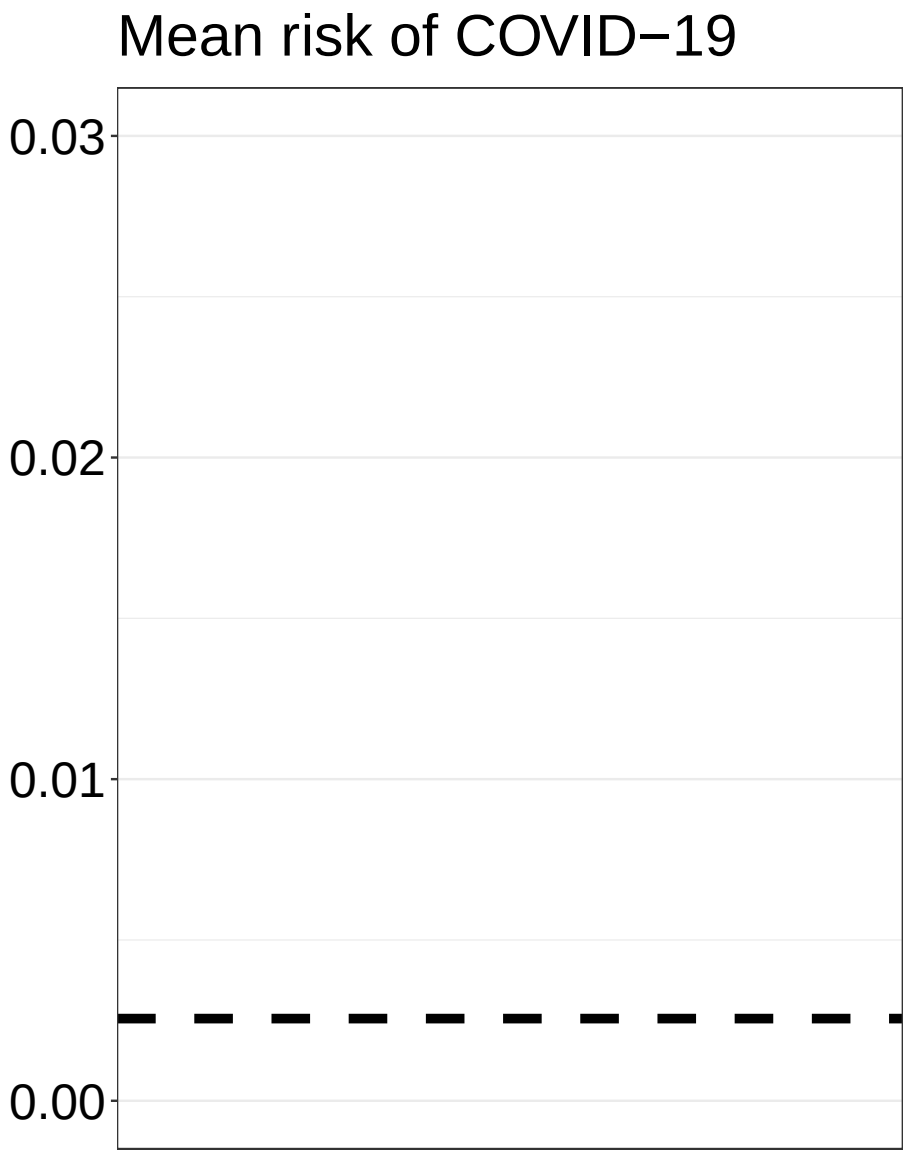
Disease risk under shifted immunogenic responses





Disease risk under shifted immunogenic responses





Stochastic interventions define the causal effects of shifts

- Stochastic interventions modify the value S would naturally assume by *shifting* the natural exposure distribution.
- Díaz and van der Laan (2012; 2018)'s shift interventions[1]

$$d(s, l) = \begin{cases} s + \delta, & s + \delta < u(l) \quad \text{(if plausible)} \\ s, & s + \delta \geq u(l) \quad \text{(otherwise)} \end{cases}$$

- Our estimand is $\psi_{0,\delta} := \mathbb{E}_{P_{\delta,0}}\{Y^{d(S,L)}\}$, which is identified by

$$\psi_{0,\delta} = \int_{\mathcal{L}} \int_{\mathcal{S}} \mathbb{E}_{P_0}\{Y \mid S = d(s, l), L = l\} \\ g_{0,S}(s \mid L = l) q_{0,L}(l) d\mu(s) d\nu(l)$$

[1] Haneuse and Rotnitzky (2013) introduced modified treatment policies.

Causal interpretation of statistical target parameter

Assumption 1: *Stable unit treatment value (SUTVA)*

- $Y_i^{d(s_i,l_i)}$ *does not depend on* $d(s_j, l_j)$ *for* $i = 1, \ldots, n$ *and* $j \neq i$*, or lack of interference (Cox 1958, Rubin 1974)*
- $Y^{d(s,l)} = Y$ *in the event* $S = d(s, l)$*, for* $i = 1, \ldots, n$

Assumption 2: *No unmeasured confounding*

$Y^{d(s,l)} \perp\!\!\!\perp S \mid L = l$*, for* $i = 1, \ldots, n$

Assumption 3: *Structural positivity*

$s \in \mathcal{S} \implies d(s, l) \in \mathcal{S}$ *for all* $l \in \mathcal{L}$*, where* $\mathcal{S}$ *denotes the support of* S *conditional on* $L = l$ *for all* $i = 1, \ldots, n$

Interpreting the causal effects of shift interventions

- Consider a data structure: $(Y_s, s \in \mathcal{S})$.
- Let $Y_s = \beta_0 + \beta_1 s + \epsilon_s$, with error $\epsilon_s \sim \mathsf{N}(0, \sigma_s^2)\ \forall\ s \in S$.
- For the counterfactual outcomes $(Y_{s'+\delta}, Y_{s'})$, their difference $Y_{s'+\delta} - Y_{s'}$ may be expressed (for some $s' \in \mathcal{S}$)

$$\begin{aligned}
\mathbb{E}Y_{s'+\delta} - \mathbb{E}Y_{s'} &= [\beta_0 + \beta_1(s' + \delta) + \cancel{\mathbb{E}\epsilon_{s'+\delta}}] - [\beta_0 + \beta_1 s' + \cancel{\mathbb{E}\epsilon_{s'}}] \\
&= \cancel{\beta_0 - \beta_0} + \cancel{\beta_1 s' - \beta_1 s'} + \beta_1 \delta \\
&= \beta_1 \delta
\end{aligned}$$

- A *unit shift* for $s' \in S$ (i.e., for $\delta = 1$) *causes* a counterfactual difference in Y of magnitude β_1 in this simple schematic.

Stochastic–interventional vaccine efficacy (SVE)

- Statistical parameter for vaccine efficacy (VE) estimands:

$$\begin{aligned}\mathrm{SVE}(\delta) &= 1 - \frac{\mathbb{E}[\mathbb{P}(Y = 1 \mid S = d(s, l), A = 1, L = l)]}{\mathbb{P}(Y = 1 \mid A = 0)} \\ &= 1 - \frac{\psi_{0,\delta}}{\mathbb{P}(Y = 1 \mid A = 0)}\end{aligned}$$

- $\mathbb{P}(Y = 1 \mid A = 0)$: counterfactual risk in the placebo arm — i.e., under randomization, $\mathbb{P}(Y = 1 \mid A = 0) \equiv \mathbb{P}(Y(0) = 1)$.
- Summarizes VE via stochastic interventions across δ, per the CoVPN immune correlates SAP[2] (Gilbert et al. 2021a;b).

[2]SAP published at `https://doi.org/10.6084/m9.figshare.13198595`.

Efficient estimation in two-phase designs

Estimation of the counterfactual mean $\psi_{0,\delta}$

A *RAL estimator* $\psi_{n,\delta}$ of $\psi_{0,\delta} := \Psi(P_0)$ is *efficient* if and only if

$$\psi_{n,\delta} - \psi_{0,\delta} = \frac{1}{n} \sum_{i=1}^{n} D^{\star}(P_0)(O_i) + o_P(n^{-1/2}) \ ,$$

where $D^{\star}(P)$ is the *efficient influence function* (EIF) of $\psi_{0,\delta}$ with respect to the nonparametric model $\mathcal{M}$ at a distribution $P \in \mathcal{M}$.

The EIF of $\psi_{0,\delta}$ is indexed by two key *nuisance parameters*

$$\overline{Q}_Y(S, L) := \mathbb{E}_P(Y \mid S, A = 1, L) \qquad \textit{outcome mechanism}$$

$$g_S(S \mid L) := f_P(S \mid A = 1, L) \qquad \textit{generalized propensity score}$$

Flexible, efficient, doubly robust estimation

- The efficient influence function of $\psi_{0,\delta}$ with respect to $\mathcal{M}$ is

$$D_F^\star(P_0)(o) = \frac{g_{0,S}(d^{-1}(s,l) \mid l)}{g_{0,S}(s \mid l)}(y - \overline{Q}_{0,Y}(s,l)) + \overline{Q}_{0,Y}(d(s,l),l) - \psi_{0,\delta}.$$

- The one-step bias-corrected estimator:

$$\psi_n^+ = \frac{1}{n}\sum_{i=1}^{n} \overline{Q}_{n,Y}(d(S_i,L_i),L_i) + D_{F,n}^\star(O_i) \ .$$

- The TML estimator updates initial estimates of $\overline{Q}_{n,Y}$ to $\overline{Q}_{n,Y}^\star$ via a tilting procedure that sets $\mathbb{E}_P D_{F,n}^\star(P_0)(O) \approx 0$:

$$\psi_n^\star = \frac{1}{n}\sum_{i=1}^{n} \overline{Q}_{n,Y}^\star(d(S_i,L_i),L_i) \ .$$

- "Double robust" – flexible modeling of nuisance parameters.

Augmented estimators for two-phase sampling designs

- Rose and van der Laan (2011) suggested inverse probability of censoring weighted (IPCW) loss functions:

$$\mathcal{L}(P_0^X)(O) = \frac{B}{g_{0,B}(Y, L)} \mathcal{L}(P_0^X)(X)$$

- When the sampling mechanism $g_{0,B}(Y, L)$ is known by design, this procedure yields a reasonably reliable estimator.
- When data-adaptive regression is warranted — that is, when $g_{0,B}(Y, L)$ is not known by design[3]— this is inefficient.

[3]Sampling of non-cases in HVTN 505 used matching (Janes et al. 2017).

Efficiency and multiple robustness (Hejazi et al. 2021)

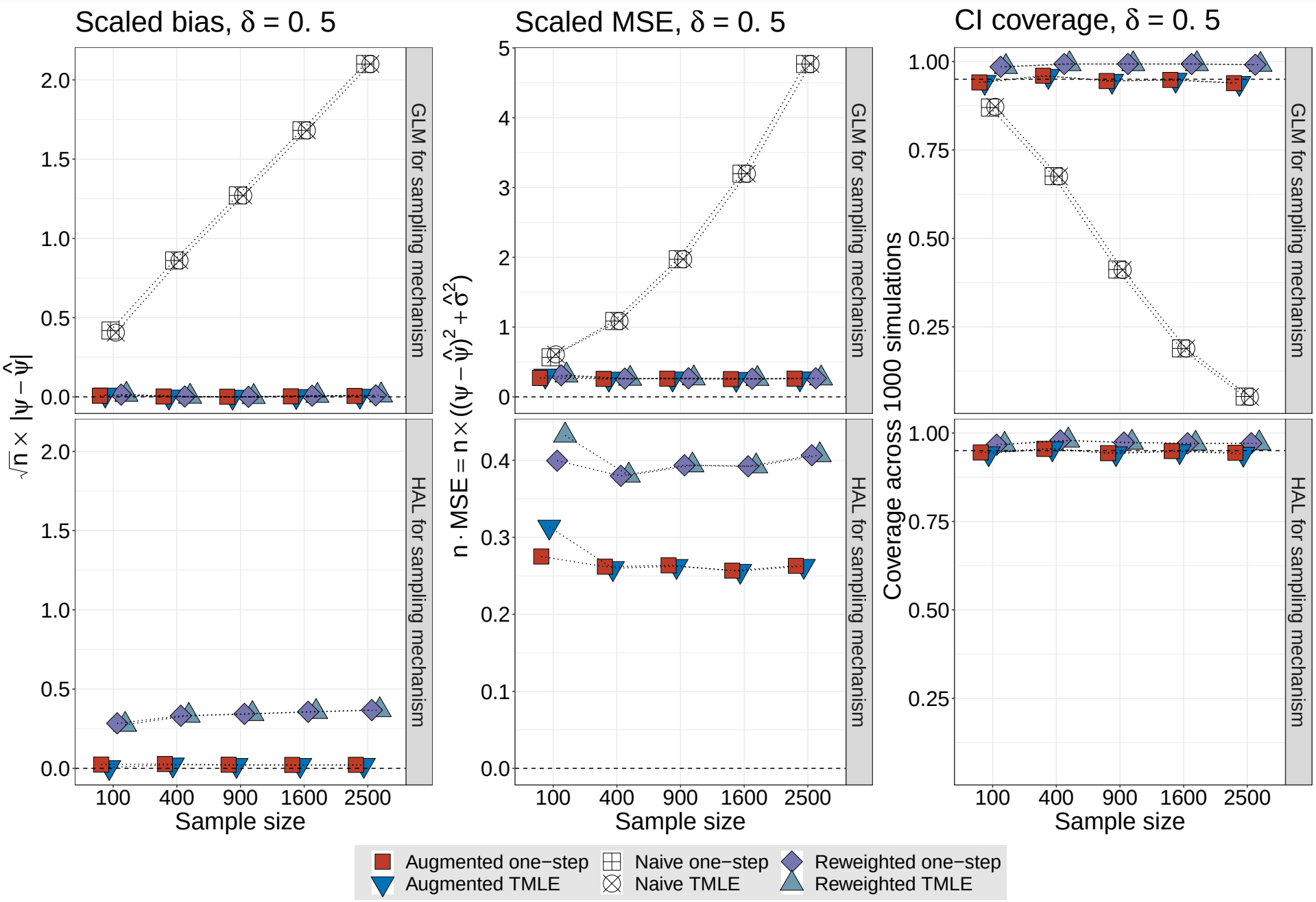
- Then, the IPCW augmentation must be applied to the EIF[4]:

$$D^\star(P_0^X)(o) = \frac{b}{g_{0,B}(y, l)} D_F^\star(P_0^X)(x) - \left(1 - \frac{b}{g_{0,B}(y, l)}\right) \mathbb{E}(D_F^\star(P_0^X)(x) \mid B = 1, Y = y, L = l) \ .$$

- Expresses observed data EIF $D^\star(P_0^X)(o)$ via complete data EIF $D_F^\star(P_0^X)(x)$; inclusion of second term improves efficiency.
- An emergent robustness property — one each of $g_{0,S}(S \mid L)$, $\overline{Q}_{0,Y}(S, L)$ and $g_{0,B}(Y, L)$, $\mathbb{E}(D_F^\star(P_0^X)(x) \mid B = 1, Y, L)$.
- Our `txshift` `R` package implements our estimators of $\psi_{0,\delta}$.

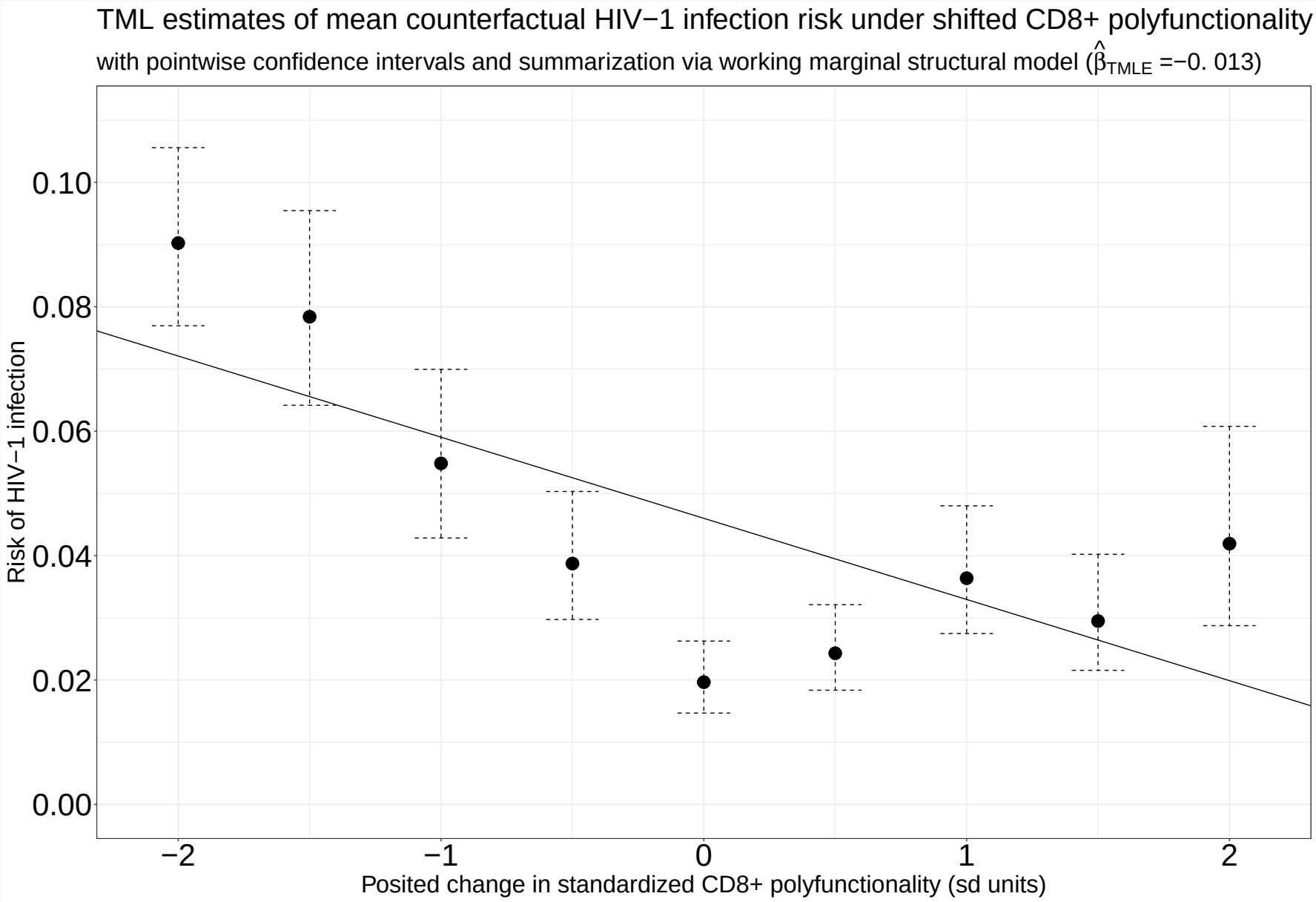
[4] Robins et al. (1994) explored a similar correction for related sampling designs.

Comparing reweighted and augmented estimators



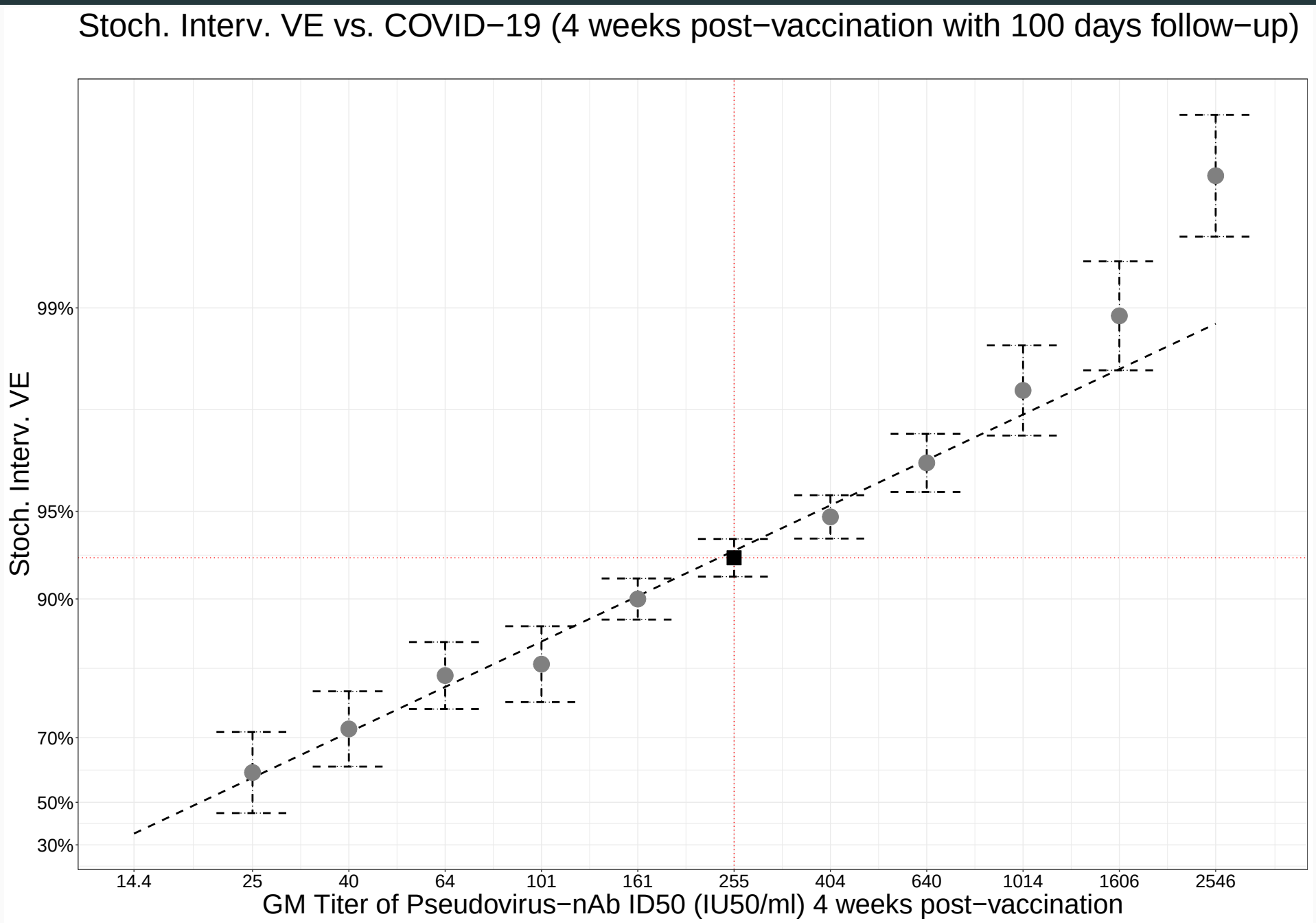
Predicting and bridging vaccine efficacy

SVE *prediction* of HIV-1 risk in the HVTN 505 trial

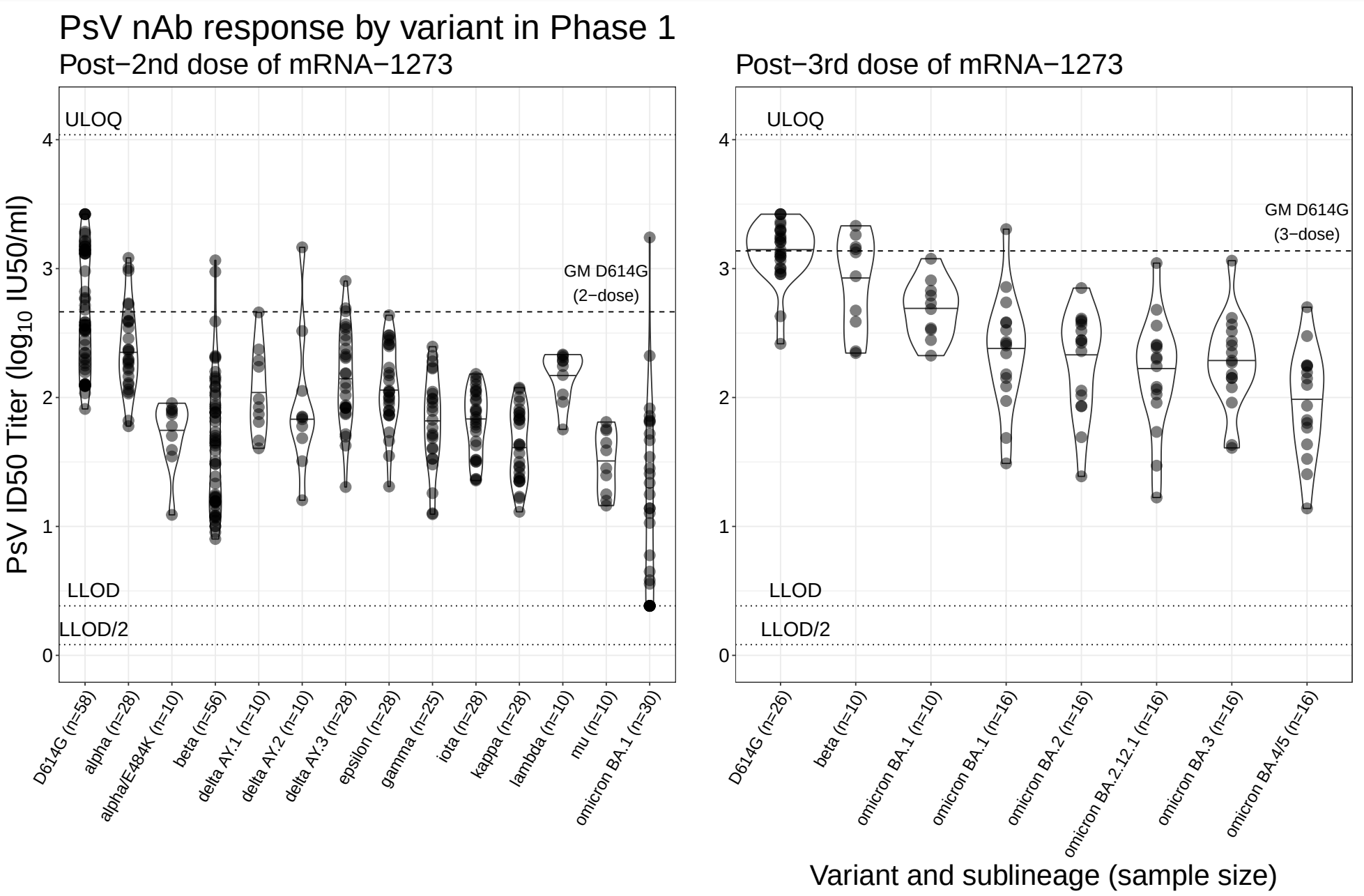


HIV-1 risk change across CD8+ score (`txshift` `R` package).

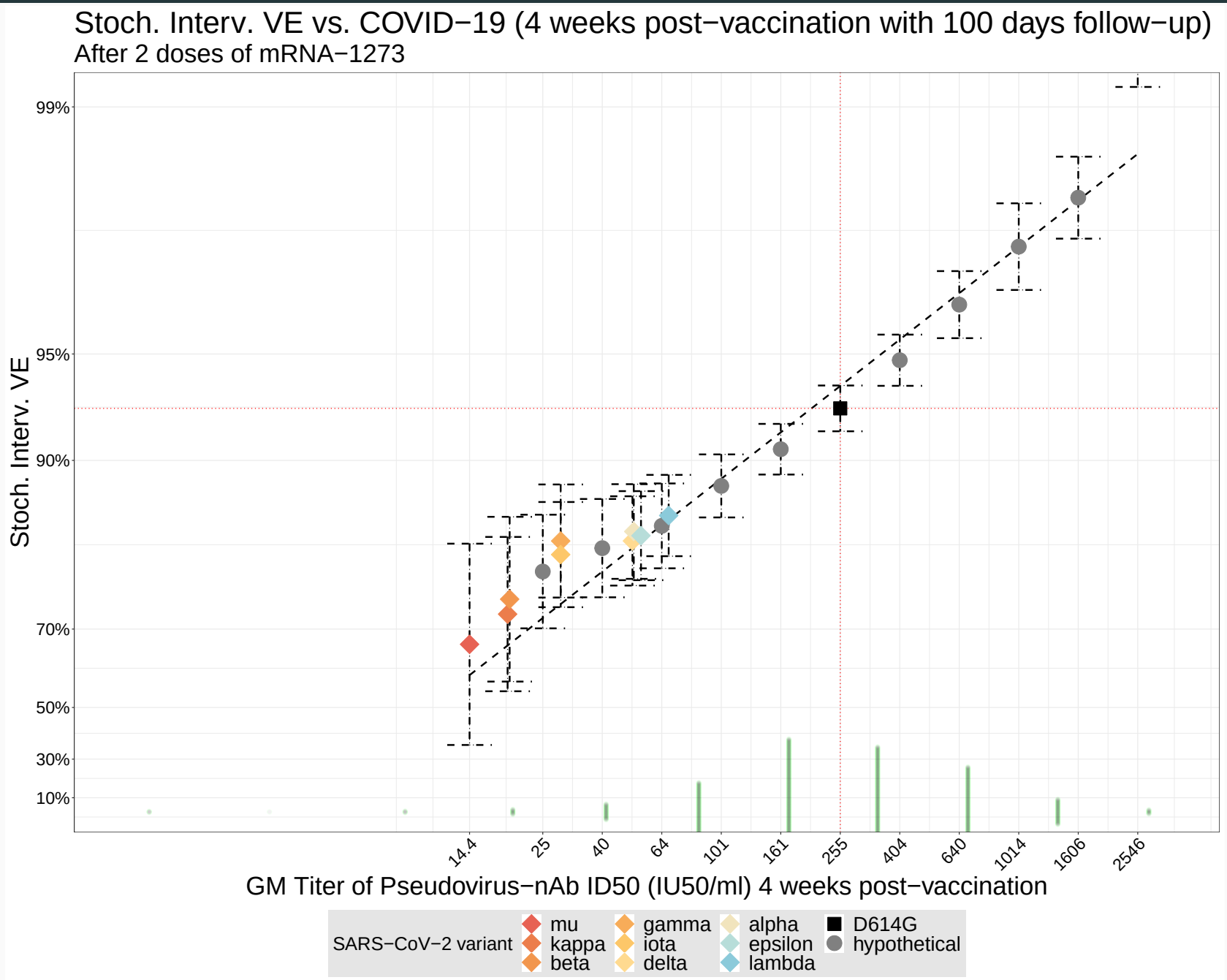
SVE *prediction* of mRNA-1273 VE in the CoVPN COVE trial



Pooled phase 1 studies: PsV nAb responses across variants



SVE *bridging* of mRNA-1273 VE (Hejazi et al. 2023)



The Big Picture

- Flexible stochastic interventions help to formulate novel modified treatment policies (based on "natural" treatment conditions).
- *Modified treatment policies* address causal questions about *realistic* manipulations of quantitative intervention variables.
- Large-scale vaccine trials routinely use two-phase designs — but need to adjust (carefully!) for resultant sampling bias.
- Efficient estimators with double/multiple robustness can safely answer such questions *while* incorporating machine learning.
- Open source software for such statistical analyses is critical for the methods to have any impact on real-world studies.

Thank you!

Thanks for listening. Any questions?

- https://nimahejazi.org
- https://github.com/nhejazi
- https://twitter.com/nshejazi
- https://doi.org/10.1111/biom.13375
- Hejazi et al. (2023) to appear in *IJID*

Appendix

Immune correlates of protection (Plotkin and Gilbert 2012)

- Correlate of Protection (CoP): immune marker statistically predictive of vaccine efficacy, not necessarily mechanistic.
- Mechanistic CoP (mCoP): immune marker that is causally and mechanistically responsible for protection.
- Nonmechanistic CoP (nCoP): immune marker that is predictive but not a causal agent of protection.
- A CoP is a *candidate surrogate* endpoint (Prentice 1989) — primary endpoint in future trials if reliably predictive.

Literature: Díaz and van der Laan (2012; 2018)

- *Proposal:* Evaluate outcome under an altered *intervention distribution* — e.g., $P_\delta(g_{0,S})(S = s \mid L) = g_{0,S}(s - \delta(L) \mid L)$.
- Identification conditions for a statistical parameter of the counterfactual outcome $\psi_{0,\delta}$ under such an intervention.
- Show that the causal quantity of interest $\mathbb{E}_{P_0^\delta}\{Y_{d(S,L)}\}$ is identified by a functional of the distribution of O, i.e.,

$$\psi_{0,\delta} = \int_{\mathcal{L}} \int_{\mathcal{S}} \mathbb{E}_{P_0}\{Y \mid S = d(s, l), L = l\} \\ g_{0,S}(s \mid L = l) \cdot q_{0,L}(l) d\mu(s) d\nu(l)$$

Literature: Haneuse and Rotnitzky (2013)

- *Proposal:* Characterization of stochastic interventions as *modified treatment policies* (MTPs).
- Assumption of *piecewise smooth invertibility* allows for the post-intervention distribution of any MTP to be recovered:

$$g_{0,S}(s \mid l; \delta) = \sum_{j=1}^{J(l)} \mathbb{I}_{\delta,j}\{h_j(s,l), l\} g_{0,S}\{h_j(s,l) \mid l\} h_j'(s,l)$$

- MTPs account for the natural value of exposure S yet may be interpreted as imposing an altered intervention mechanism.

Slope in a semiparametric model

- Consider the stochastic intervention $g_\delta(\cdot \mid L)$:

$$\begin{aligned}\mathbb{E}Y_{g_\delta} &= \int_L \int_s \mathbb{E}(Y \mid S = s, L) g(s - \delta \mid L) ds dP_0(L) \\ &= \int_L \int_z \mathbb{E}(Y \mid S = z + \delta, L) g(z \mid L) dz dP_0(L),\end{aligned}$$

  defning the change of variable $z = s - \delta$.

- For a semiparametric model, $\mathbb{E}(Y \mid S = z, L) = \beta z + \theta(L)$:

$$\begin{aligned}\mathbb{E}Y_{g_\delta} - \mathbb{E}Y &= \int_L \int_z [\mathbb{E}(Y \mid S = z + \delta, L) - \mathbb{E}(Y \mid S = z, L)] \\ &\qquad g(z \mid L) dz dP_0(L) \\ &= [\beta(z + \delta) + \theta(L)] - [\beta z + \theta(L)] \\ &= \beta\delta\end{aligned}$$

Flexible conditional density estimation of $g_{0,S}$

- Díaz and van der Laan (2011)'s conditional density estimator:

$$g_{n,\alpha}(s \mid L) = \frac{\mathbb{P}(s \in [\alpha_{t-1}, \alpha_t) \mid L)}{\alpha_t - \alpha_{t-1}}.$$

  - Re-expressed as hazard regressions in repeated measures data.
  - Tuning parameter $t \approx$ bandwidth in kernel density estimation.

- When càdlàg (RCLL) with finite sectional variation, we have

$$\text{logit}\{\mathbb{P}(s \in [\alpha_{t-1}, \alpha_t) \mid L)\} = \beta_0 + \sum_{w \subset \{1,\ldots,d\}} \sum_{i=1}^{n} \beta_{w,i} \phi_{w,i},$$

for appropriate basis functions $\{\phi_{w,i}\}_{i=1}^{n}$ (Gill et al. 1995).

Flexible conditional density estimation of $g_{0,S}$

- Utilizing a particular basis construction for ϕ_w, van der Laan (2017)'s HAL estimator achieves $n^{-1/4}$ convergence rate[5].
- Loss-based cross-validation allows selection of a suitable HAL estimator, which has only the ℓ_1 regularization term λ:

$$\beta_{n,\lambda} = \underset{\beta:|\beta_0|+\sum_{w\subset\{1,\ldots,d\}}\sum_{i=1}^{n}|\beta_{w,i}|<\lambda}{\arg\min} P_n\mathcal{L}(g_{\beta,\lambda,S}),$$

  where $\mathcal{L}(\cdot)$ is an appropriate loss function, giving $\{\lambda_n, \beta_n\}$.

- We denote by $g_{n,\lambda,S} := g_{\beta_{n,\lambda},S}$, the HAL estimate of $g_{0,S}$.
- Our `haldensify` `R` package implements our estimator of $g_{0,S}$.

[6]Similar rates can be achieved via *local* (vs. global) smoothness assumptions on $g_{n,S}$ (see, e.g., Robins et al. 2008, Mukherjee et al. 2017, Liu et al. 2021).

A useful class of functions

Consider space of *cadlag* functions with *finite variation norm*.

Def. cadlag = *left-hand continuous* with *right-hand limits*

Variation norm Let $\theta_s(u) = \theta(u_s, 0_{s^c})$ be the *section* of θ that sets the coordinates in *s equal to zero*.

The *variation norm* of θ can be written:

$$|\theta|_v = \sum_{s \subset \{1,\ldots,d\}} \int | \, d\theta_s(u_s) \, |,$$

where $x_s = (x(j) : j \in s)$ and the sum is over all subsets.

Sectional variation norm

We can represent the function θ as

$$\theta(x) \quad = \quad \theta(0) + \sum_{s \subset \{1,\ldots,d\}} \int \mathbb{I}(x_s \geq u_s) d\theta_s(u_s),$$

For discrete measures $d\theta_s$ with *support points* $\{u_{s,j} : j\}$ we get a *linear combination* of indicator *basis functions*:

$$\theta(x) = \theta(0) + \sum_{s \subset \{1,\ldots,d\}} \sum_j \beta_{s,j} \theta_{u_{s,j}}(x),$$

where $\beta_{s,j} = d\theta_s(u_{s,j})$, $\theta_{u_{s,j}}(x) = \mathbb{I}(x_s \geq u_{s,j})$, and

$$|\theta|_v = \theta(0) + \sum_{s \subset \{1,\ldots,d\}} \sum_j |\beta_{s,j}|.$$

Convergence rate for HAL estimators

We have, for $\alpha(d) = 1/(d+1)$,

$$|\theta_{n,M} - \theta_{0,M}|_{P_0} = o_P(n^{-(1/4+\alpha(d)/8)}).$$

Thus, if we select $M > |\theta_0|_v$, then

$$|\theta_{n,M} - \theta_0|_{P_0} = o_P(n^{-(1/4+\alpha(d)/8)}) \ .$$

Due to oracle inequality for the cross-validation selector M_n,

$$|\theta_{n,M_n} - \theta_0|_{P_0} = o_P(n^{-(1/4+\alpha(d)/8)}) \ .$$

Improved convergence rate (Bibaut and van der Laan 2019):

$$|\theta_{n,M_n} - \theta_0|_{P_0} = o_P(n^{-1/3} \log(n)^{d/2}) \ .$$

Algorithm for TML estimation

1. Construct initial estimators $g_{n,S}$ of $g_{0,S}(S, L)$ and $Q_{n,Y}$ of $\overline{Q}_{0,Y}(S, L)$, perhaps using data-adaptive regression techniques.
2. For each observation i, compute an estimate $H_n(s_i, l_i)$ of the auxiliary covariate $H_0(s_i, l_i)$.
3. Estimate the parameter ϵ in the logistic regression model

$$\text{logit}\overline{Q}_{\epsilon,n,Y}(s, l) = \text{logit}\overline{Q}_{n,Y}(s, l) + \epsilon H_n(s, l),$$

   or an alternative regression model incorporating weights.
4. Compute TML estimator Ψ_n of the target parameter, defining the update $\overline{Q}^{\star}_{n,Y}$ of the initial estimate $\overline{Q}_{n,Y}$ to $\overline{Q}_{\epsilon_n,n,Y}$:

$$\Psi_n = \Psi(P^{\star}_n) = \frac{1}{n}\sum_{i=1}^{n}\overline{Q}^{\star}_{n,Y}(d(S_i, L_i), L_i).$$

Algorithm for IPCW-TML estimation

1. Using all observed units, estimate the sampling mechanism $g_{0,B}(Y, L)$, perhaps using data-adaptive regression methods.
2. Using only observed units in the phase-two sample $B = 1$, construct initial estimators $g_{n,S}(S, L)$ and $\overline{Q}_{n,Y}(S, L)$, weighting by the sampling mechanism estimate $g_{n,B}(Y, L)$.
3. With the approach described for the full data case, compute $H_n(s_i, l_i)$, and fluctuate submodel via logistic regression.
4. Compute IPCW-TML estimator Ψ_n of the target parameter, by solving the IPCW-augmented EIF estimating equation.
5. Iteratively update estimated sampling weights $g_{n,B}(Y, L)$ and IPCW-augmented EIF, updating TMLE in each iteration.

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