Evaluating treatment efficacy in vaccine clinical trials with two-phase designs using stochastic-interventional effects

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Immune Correlates of 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 million total cases detected globally;
  - new variants emerging, with vaccine uptake globally slowing;
  - 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 immunogenic responses differently?
- *COVE*: How would COVID-19 disease rate have differed for alternative vaccine-induced immunogenic response profiles?
- **Question**: How can [HIV-1, COVID-19] vaccines be improved through modulating immunogenic response profiles?

Why Measure and Analyze Immune Correlates?

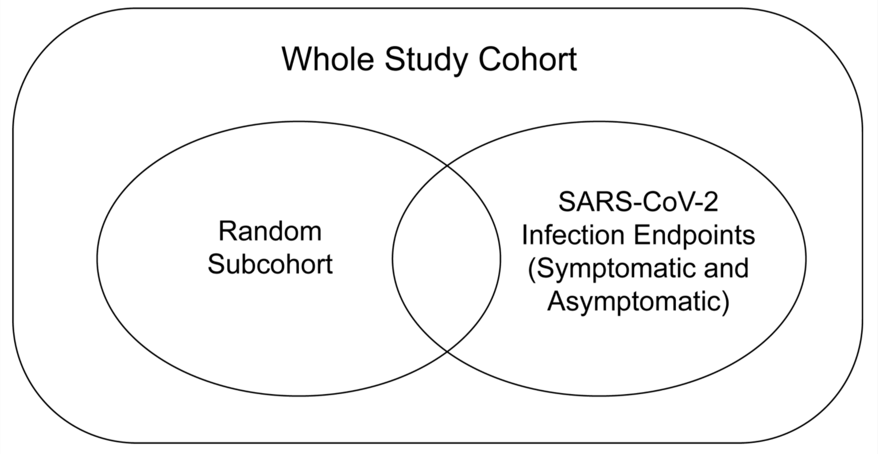
- Two, interrelated goals of vaccine correlates analyses are to
  - identify/validate possible *surrogate endpoints* (Prentice 1989);
  - understand *protective mechanisms* of vaccines.
- If an immune correlate is established to reliably predict VE, subsequent efficacy trials may use it as a primary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

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*: second-phase 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 $O = (B, BX) = (L, B, BS, Y) \sim P_0 \in \mathcal{M}$.
  - $B \in \{0, 1\}$ indicates inclusion in the second-phase sample.
  - $\pi_0 := \mathbb{P}(B = 1 \mid Y, L)$ must be *known by design* or estimated.
  - Implicitly conditioning on the vaccine arm: $O = \{X \mid A = 1\}$.

Causal Effects for Quantitative Exposures

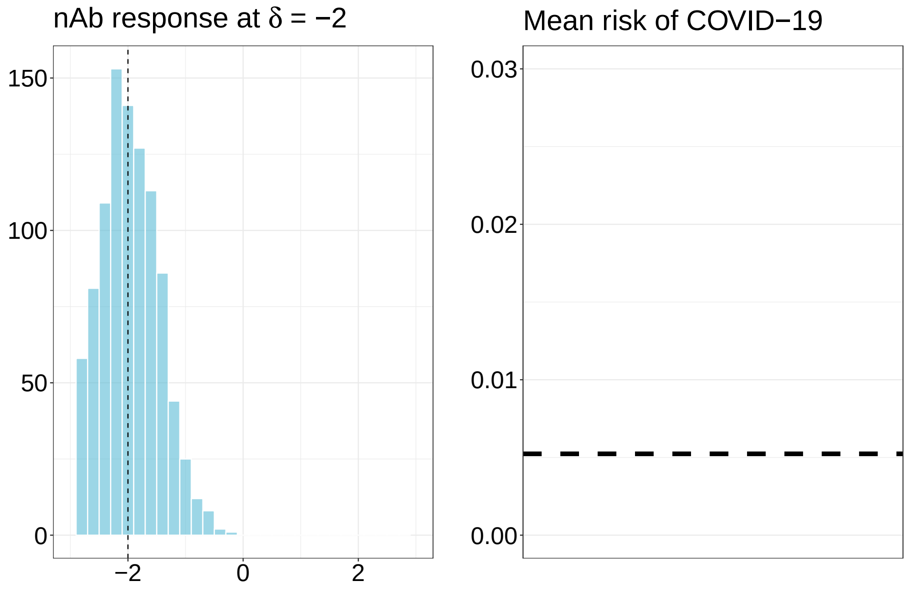
Static Interventions Aren't Enough

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

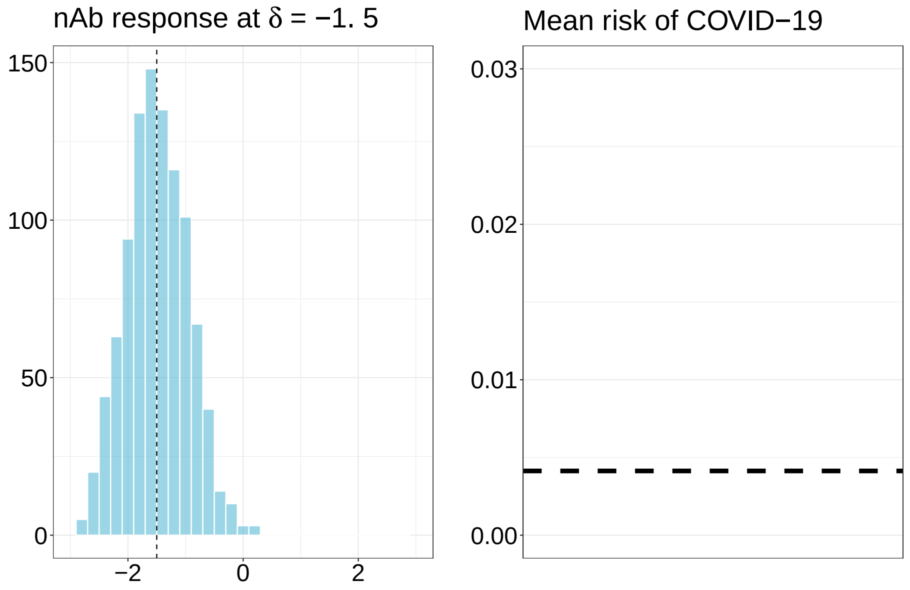
  $$L = f_L(U_L); A \sim \text{Bern}(0.5); S = f_S(A, L, U_S); Y = f_Y(S, A, L, U_Y)$$

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

Disease Risk Under Shifted Immunogenic Responses



Disease Risk Under Shifted Immunogenic Responses



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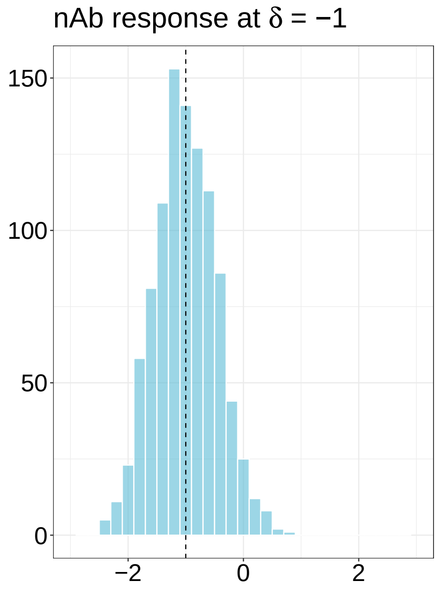
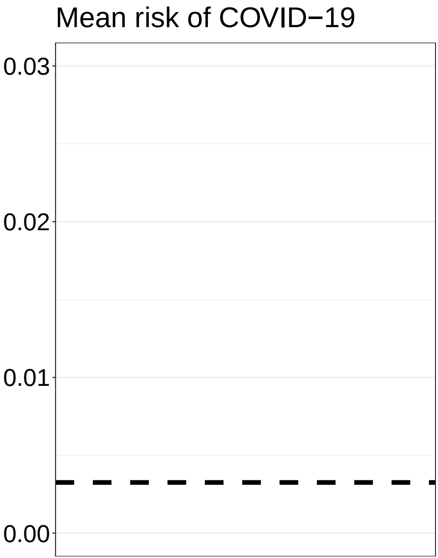
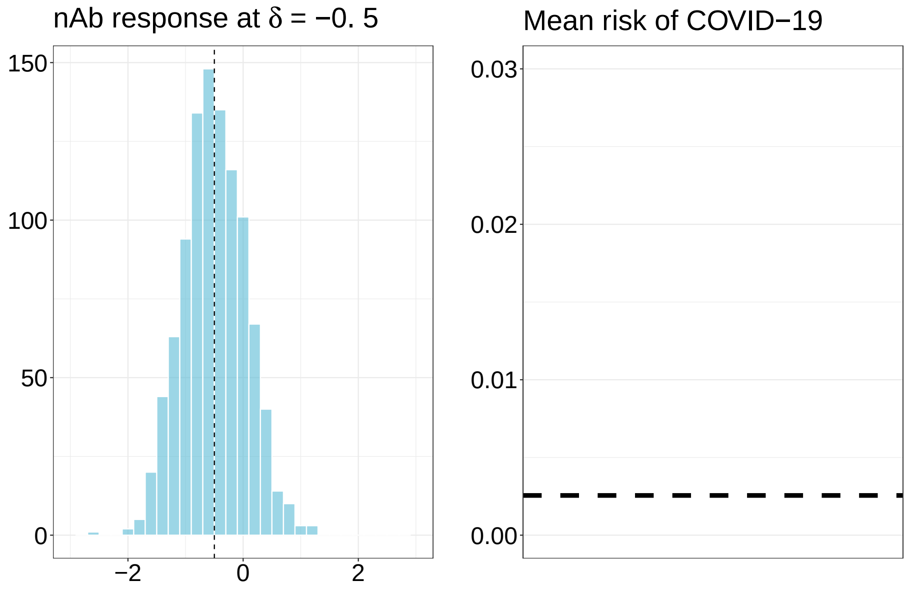




Disease Risk Under Shifted Immunogenic Responses



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 $\psi_{0,\delta} := \mathbb{E}_{P_0^\delta}\{Y_{d(S,L)}\}$, 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.

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 $\epsilon_s \sim N(0, \sigma_s^2)$ $\forall s \in S$.
- For the counterfactual outcomes $(Y_{s'+\delta}, Y_{s'})$, their difference $Y_{s'+\delta} - Y_{s'}$ may be expressed (for some $s' \in \mathcal{S}$)

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

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

Stochastic–Interventional Vaccine Efficacy

- Causal parameter based on vaccine efficacy (VE) estimands:

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

- $\mathbb{P}(Y(0) = 1)$: counterfactual infection risk in the placebo arm — under randomization, $\mathbb{P}(Y(0) = 1) \equiv \mathbb{P}(Y = 1 \mid A = 0)$.
- 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 $\psi_{0,\delta}$

An *estimator* $\psi_{n,\delta}$ of $\psi_{0,\delta} \coloneqq \Psi(P_0)$ is *efficient* if and only if

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

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.

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

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

$$g_S(S \mid L) \coloneqq p(S \mid L) \qquad \textit{generalized propensity score}$$

Flexible, Efficient, Doubly Robust Estimation

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

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

- The one-step bias-corrected estimator:

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

- The TML estimator updates initial estimates of $\overline{Q}_n$ by tilting:

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

- Both doubly robust: flexible modeling for nuisance estimation.

Augmented Estimators for Two-Phase Sampling Designs

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

$$\mathcal{L}(P_0^X)(O) = \frac{B}{\pi_0(Y, L)} \mathcal{L}(P_0^X)(X)$$

- When the sampling mechanism $\pi_0(Y, L)$ is known by design, this procedure yields a reasonably reliable estimator.
- When data-adaptive regression must be used — that is, when $\pi_0(Y, L)$ is not known by design[3]— this is insufficient.

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

Efficiency and Multiple Robustness (Hejazi et al. 2020)

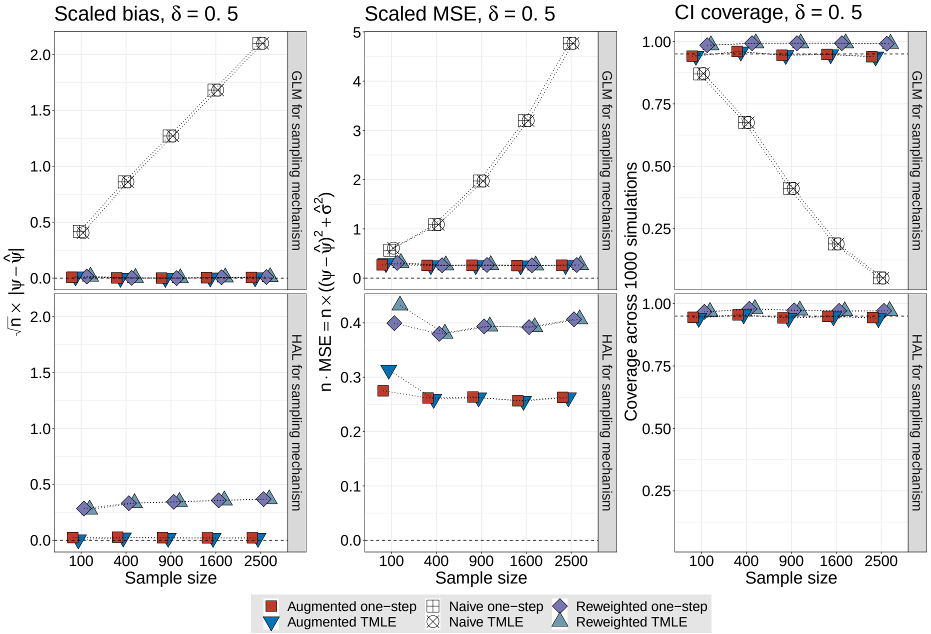
- Then, the IPCW augmentation must be applied to the EIF[4]:

$$D^{\star}(P_0^X)(o) = \frac{b}{\pi_0(y, l)} D_F^{\star}(P_0^X)(x) - \left(1 - \frac{b}{\pi_0(y, l)}\right) \mathbb{E}(D_F^{\star}(P_0^X)(x) \mid B = 1, Y = y, L = l).$$

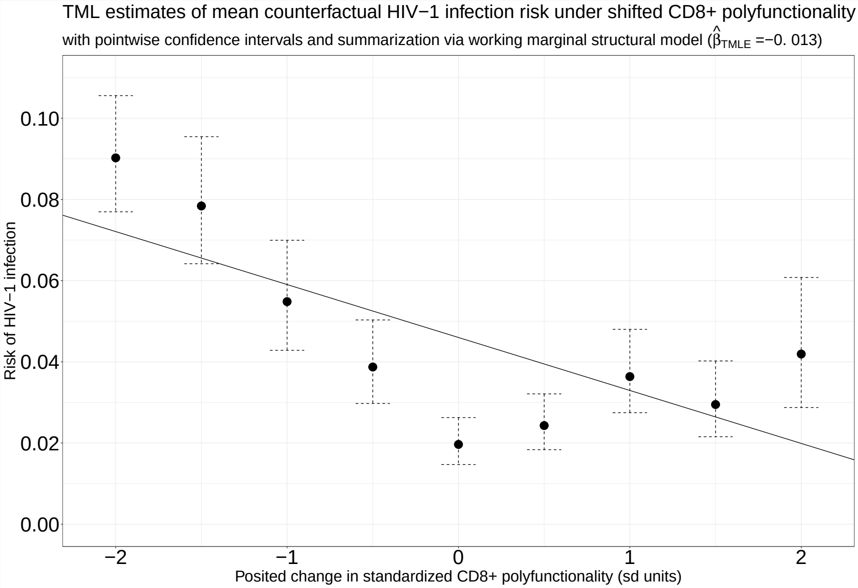
- Expresses observed data EIF $D^{\star}(P_0^X)(o)$ via complete data EIF $D_F^{\star}(P_0^X)(x)$; inclusion of second term improves efficiency.
- An emergent multiple robustness property — combinations of $\{g_0(S \mid L), \overline{Q}_0(S, L)\} \times \{\pi_0(Y, L), \mathbb{E}(D_F^{\star}(P_0^X)(x) \mid B = 1, Y, L)\}$.
- Our `txshift` `R` package implements our estimators of $\psi_{0,\delta}$.

[4] A very general version appears to have been presented in Robins et al. (1994).

Comparing Reweighted and Augmented Estimators

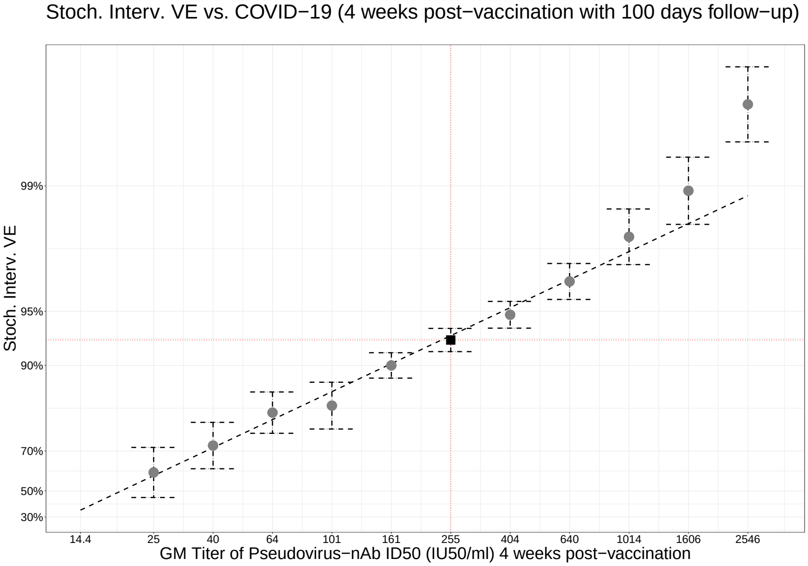


SVE Prediction of HIV-1 Risk thru CD8+ Immune Response



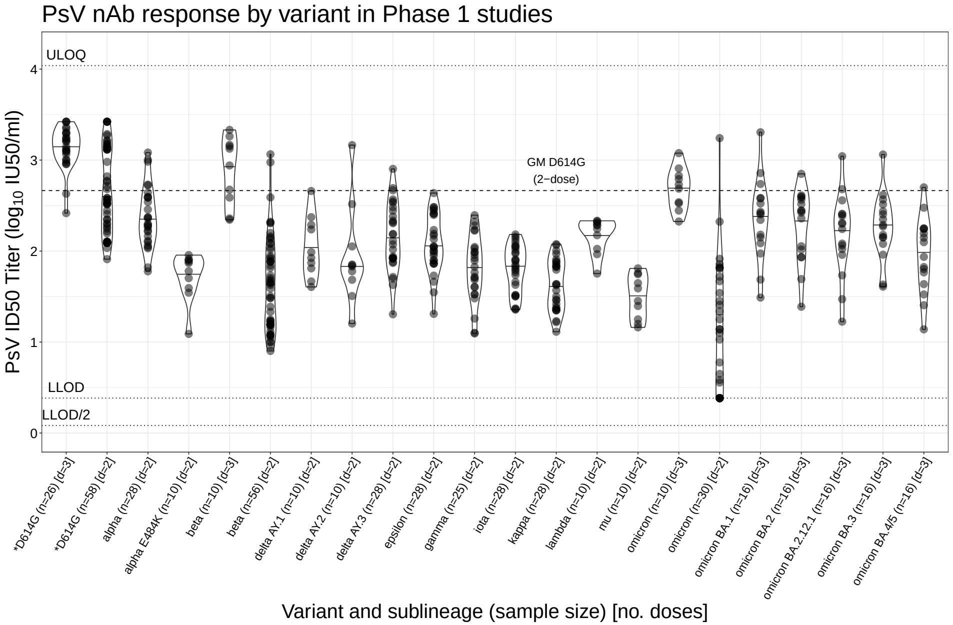
HIV-1 risk change across CD8+ response (`txshift` R package).

SVE Prediction of mRNA-1273 VE thru PsV nAb Correlate

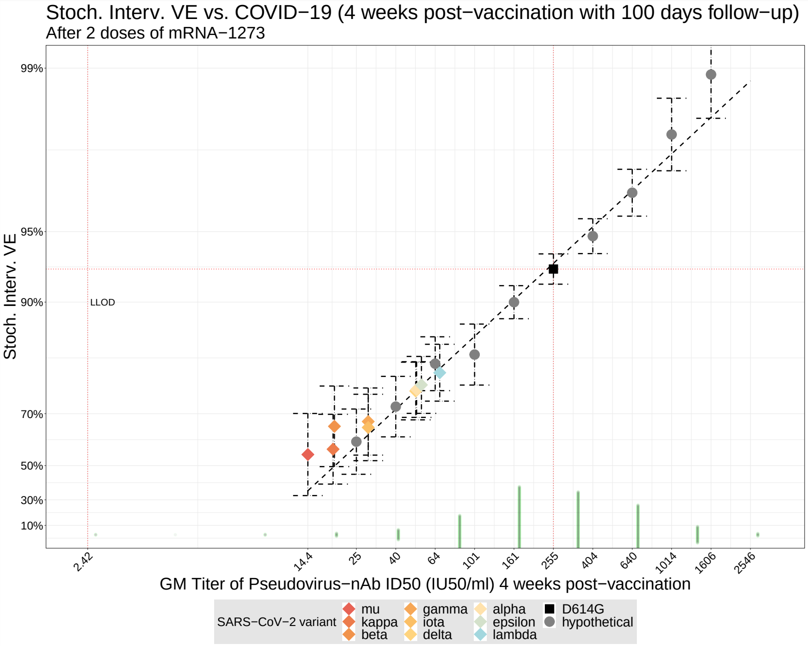


Bridging VE Using Immune Correlates

Pooled Phase 1 Studies: PsV nAb Responses Across Variants



SVE Bridging of mRNA-1273 VE thru PsV nAb Correlate

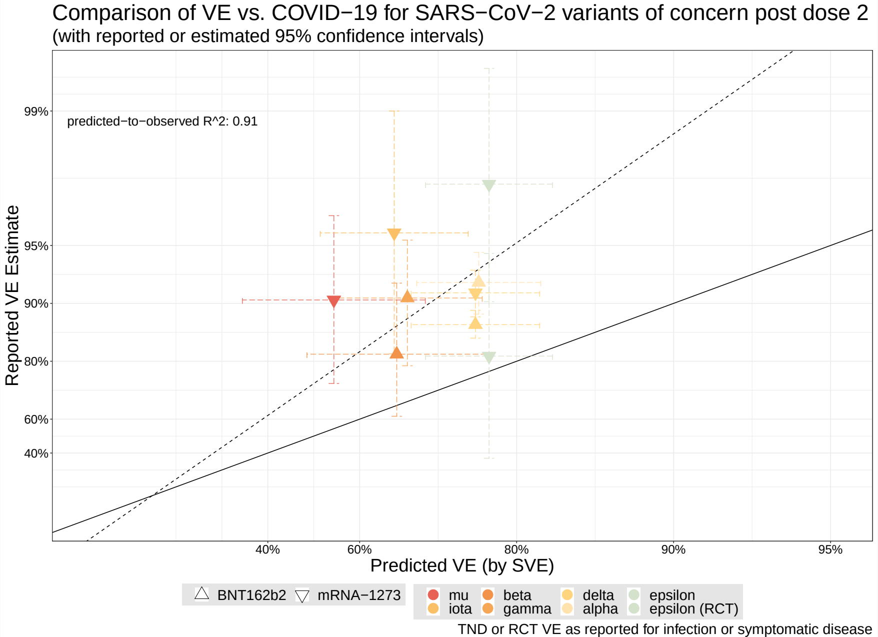


SVE Predictions vs. Real-World Reported Estimates

- Compared δ-calibrated SVE predictions to reported VE estimates, from TND studies or RCTs.
- Inclusion/exclusion criteria for TND-based VE estimates[5]:
  - VE estimated by direct measurement of SARS-CoV-2 variants.
  - Reported VE estimates for mRNA vaccines (BNT162b2 or mRNA-1273), studying VE 2–6 months post-2$^{\text{nd}}$ dose.
  - Allowed flexibility in choice of dosing interval, with some studies extending to 12 weeks between doses.
- Studied concordance of SVE predictions and reported (TND or RCT) estimates of VE following most recent vaccine dose.

[5] Comparison of TND studies performed in collaboration with Dr. Lindsay Carpp.

Concordance of SVE Predictions and Reported VE Estimates



Summary of SVE Prediction for Immunobridging

- SVE prediction shows sharp changes in VE with shifts to the GM titer of the PsV nAb correlate in vaccinees.
- Bridging VE across variants indicates VE drops but stabilizes at 50%, if the model based on ancestral D614G strain holds.
- Post-2$^{\text{nd}}$ dose: For most variants (excepting omicron), the VE estimate ranges from 50% (mu) to 80% (epsilon).
- SVE predictions and real-world VE estimates well-correlated, but SVE predictions may be underestimates, as PsV nAb correlate is an *imperfect* causal *mediator* of total VE.

The Big Picture

- Stochastic interventions provide a framework for formulating novel policies based on natural treatment conditions.
- These modified treatment policies address causal questions about *realistic* interventions on quantitative treatments.
- Large-scale vaccine trials rely upon two-phase designs — but need to (very carefully!) adjust for the 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?

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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.

From the Causal to the 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)*
- $Y^{d(s,l)} = Y$ *in the event* $S = d(s, l)$*, for* $i = 1, \ldots, n$

Assumption 2: *No Unmeasured Confounding*

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

Assumption 3: *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* $i = 1, \ldots n$

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:

$$g_{0,S}(s \mid l; \delta) = \sum_{j=1}^{J(l)} \mathbb{I}_{\delta,j}\{h_j(s,l), l\} g_0\{h_j(s,l) \mid l\} h_j'(s,l)$$

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

A Linear Modeling Perspective

- Briefly consider a simple data structure: $X = (Y, S)$; we seek to model the outcome Y as a function of S.
- Linear model: consider $Y_i = \beta_0 + \beta_1 S_i + \epsilon_i$, with error $\epsilon_i \sim N(0, 1)$.
- Letting δ be a change in S, $Y_{S+\delta} - Y_S$ may be expressed

$$\begin{aligned}
\mathbb{E}Y_{S+\delta} - \mathbb{E}Y_S &= [\beta_0 + \beta_1(\mathbb{E}S + \delta)] - [\beta_0 + \beta_1(\mathbb{E}S)] \\
&= \beta_0 - \beta_0 + \beta_1\mathbb{E}S - \beta_1\mathbb{E}S + \beta_1\delta \\
&= \beta_1\delta
\end{aligned}$$

- So, a *unit shift* in S (i.e., $\delta = 1$) induces a change in the difference in outcomes of magnitude β_1.

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

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

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[6].
- 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 $g_{n,\lambda,S} \coloneqq g_{\beta_{n,\lambda},S}$, 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.

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 of HAL

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 of $g_0(S, L)$ and Q_n of $\overline{Q}_0(S, L)$, perhaps using data-adaptive regression techniques.
2. For each observation i, compute an estimate $H_n(s_i, l_i)$ of the auxiliary covariate $H(s_i, l_i)$.
3. Estimate the parameter ϵ in the logistic regression model
$$\text{logit}\overline{Q}_{\epsilon,n}(s, l) = \text{logit}\overline{Q}_n(s, l) + \epsilon H_n(s, l),$$
or an alternative regression model incorporating weights.
4. Compute TML estimator Ψ_n of the target parameter, defining update $\overline{Q}_n^{\star}$ of the initial estimate $\overline{Q}_{n,\epsilon_n}$:
$$\Psi_n = \Psi(P_n^{\star}) = \frac{1}{n}\sum_{i=1}^{n} \overline{Q}_n^{\star}(d(S_i, L_i), L_i).$$

Algorithm for IPCW-TML Estimation

1. Using all observed units (X), estimate sampling mechanism $\pi(Y, L)$, perhaps using data-adaptive regression methods.
2. Using only observed units in the second-stage sample $C = 1$, construct initial estimators $g_n(S, L)$ and $\overline{Q}_n(S, L)$, weighting by the sampling mechanism estimate $\pi_n(Y, L)$.
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 $\pi_n(Y, L)$ and IPCW-augmented EIF, updating TMLE in each iteration.

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