Evaluating Immune Correlates of Protection in Vaccine Efficacy Trials with Stochastic-Interventional Causal Effects

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OVERVIEW

- Vaccine research aims to characterize and validate immune correlates of protection (CoPs), to elucidate immunologic mechanisms and to serve as surrogate endpoints.
- Four statistical frameworks advanced to evaluate candidate CoPs in RCTs [1].
- We present one such method, *stochastic-interventional vaccine efficacy* (SVE) [2], based on the causal effects of modified treatment policies (MTPs) [3, 4] applied to CoPs.
- The `txshift R` package [5] implements efficient estimators of counterfactual mean of an MTP, with corrections for outcome-dependent, two-phase sampling [6].

COVPN VACCINE TRIALS

- COVE Phase 3 trial of Moderna vaccine (mRNA-1273) versus placebo
  - L: Baseline risk score, minority race/ethnicity indicator, high risk indicator
  - A: Randomized two doses Days 1, 29 (D1, D29)
  - S: D29, D57 measures of five candidate CoPs
  - Y: COVID-19 by 100 (129) days post-D57 (D29)
- ENSEMBLE Phase 3 trial of Janssen vaccine (Ad26.COV2.S) versus placebo
  - L: Baseline risk score, region (e.g., N. America)
  - A: Randomized single dose D1
  - S: D29 measures of three candidate CoPs
  - Y: COVID-19 by 181 days post-D29
- *Goal*: Evaluate separately candidate CoPs in the COVE and ENSEMBLE vaccine trials.

STOCHASTIC-INTERVENTIONAL VACCINE EFFICACY

- Let *ideal study data* be i.i.d. samples of $X = (L, A, S, Y) \sim \mathsf{P}_0 \in \mathcal{M}$, for P_0 an unknown data-generating distribution in the nonparametric model $\mathcal{M}$, i.e., no restrictions on the form of P_0.
  - L baseline covariates, A randomized treatment assignment (vaccine, placebo), S measure of CoP at given time point (D29, D57), and Y indicator of COVID-19 by pre-defined end of follow-up.
  - Case-cohort sampling used to measure candidate CoPs S, so only available in an outcome-dependent, two-phase sample, i.e., *observed study data* are i.i.d. samples of $O = (L, A, BS, Y, B)$, where B is a binary indicator of selection into the case-cohort sample; this necessitates incorporating a correction for estimator construction [8, 9, 6].
- SVE statistical parameter contrasts adjusted mean under an MTP against risk in placebo arm:

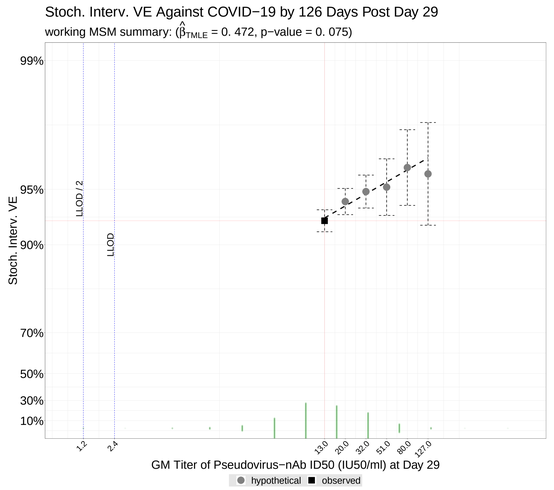
$$\psi_\delta^{\text{SVE}} \equiv \Psi_\delta^{\text{SVE}}(\mathsf{P}_0) := 1 - \frac{\mathbb{E}_L[\mathbb{P}(Y = 1 \mid S = S + \delta, A = 1, L = l) \mid A = 1, L]}{\mathbb{E}_L[\mathbb{P}(Y = 1 \mid A = 0, L = l) \mid L]}, \quad (1)$$

  where numerator is counterfactual risk under an MTP shifting S to $S + \delta$ in vaccine arm ($A = 1$) *under identification assumptions* and denominator is counterfactual risk in placebo arm ($A = 0$) *by randomization*. Identification assumptions (for numerator quantity) under NPSEM-IE include
  - *no unmeasured confounding*: $Y^{S+\delta} \perp\!\!\!\perp S \mid A = 1, L$ (possibly stronger than required, per [3]), and
  - *positivity*: $(l, s) \in \text{supp}_{\mathsf{P}_0}(L, S) \implies (l, s + \delta) \in \text{supp}_{\mathsf{P}_0}(L, S)$ for fixed δ and $A = 1$.
- The estimator $\Psi_\delta^{\text{SVE}}(\hat{\mathsf{P}}_n)$ is regular and asymptotically linear (RAL) in the model $\mathcal{M}$, admitting

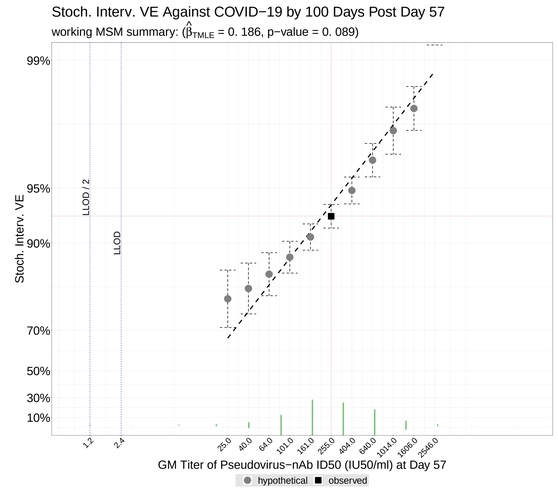
$$\sqrt{n}(\Psi_\delta^{\text{SVE}}(\hat{\mathsf{P}}_n) - \Psi_\delta^{\text{SVE}}(\mathsf{P}_0)) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} D^\star(\mathsf{P}_0)(O_i) + o_{\mathsf{P}}(1/\sqrt{n}), \quad (2)$$

  where $D^\star(\mathsf{P}_0)(O)$ is the efficient influence function (EIF) of RAL estimators of ψ_δ^{SVE} wrt $\mathsf{P}_0 \in \mathcal{M}$.
- Developed and implemented asymptotically efficient one-step and targeted minimum loss (TML) estimators [6] of $\Psi_\delta^{\text{SVE}}(\mathsf{P}_0)$, which use the EIF in distinct bias correction steps and are both
  - *doubly robust consistent* when two of four nuisance parameters are appropriately well-modeled (e.g., using ensemble machine learning [10]) such that product of convergence rates of pairs of nuisance estimators is $o_{\mathsf{P}}(1/\sqrt{n})$, and
  - *asymptotically semi-parametric efficient* when all four nuisance parameters are appropriately well-modeled.
- Applied the TML estimator of the SVE parameter, Eqn. (1), to evaluate candidate CoPs in the COVE and ENSEMBLE vaccine trials [2, 11]; results displayed for a single CoP in Figure 1.
- SVE to be available in the `vaccine R` package (`https://CRAN.R-project.org/package=vaccine`).

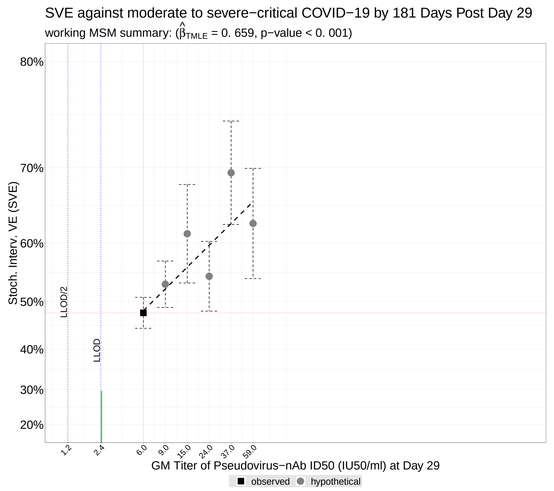
DATA ANALYSIS & RESULTS



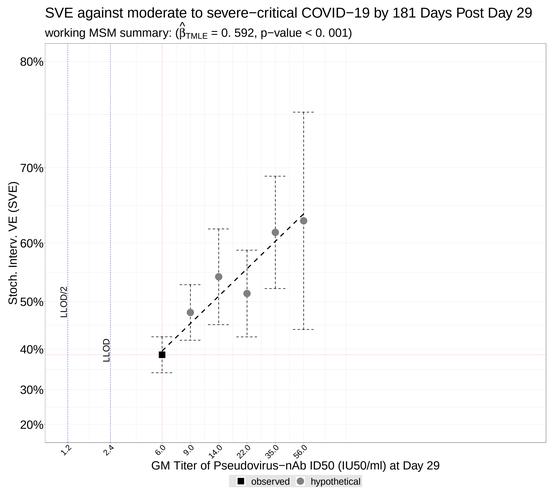
(a) SVE of D29 PsV-nAb in COVE.



(b) SVE of D57 PsV-nAb in COVE.



(c) SVE of D29 PsV-nAb in ENSEMBLE (all regions).



(d) SVE of D29 PsV-nAb in ENSEMBLE (Latin America).

Figure 1: SVE of pseudovirus neutralizing antibody (PsV-nAb) at D29, D57 in COVE (upper), ENSEMBLE (lower). TML-based point estimates (black $\delta = 0$, grey $\delta \neq 0$) with EIF-based SE estimates, summarized (dashed lines) by working MSM [7, 6]. δ chosen based on *structural positivity*: for $\delta < 0$, $S + \delta$ above assay lower detection limit (LLOD) for at least 90% of participants.

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