# Evaluating the causal impacts of vaccine-induced immune responses in two-phase vaccine efficacy trials

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## The burden of HIV-1

- The HIV-1 epidemic — the facts:
  - now in its fourth decade,
  - 2.5 million new infections occurring annually worldwide,
  - new infections outpace patients starting antiretroviral therapy.
- *Most efficacious* preventive vaccine: ∼31% reduction rate.
- **Question**: To what extent can HIV-1 vaccines be improved by modulating immunogenic CD4+/CD8+ response profiles?

## HVTN 505 trial examined new antibody boost vaccines

- HIV Vaccine Trials Network's (HVTN) 505 vaccine efficacy; randomized controlled trial, $n = 2504$ (Hammer et al. 2013).
- **Question:** How would HIV-1 infection risk in week 28 have changed had vaccine-induced immunogenic response differed?
- Immunogenic response profiles only available for second-phase sample of $n = 189$ (Janes et al. 2017) due to cost limitations.
- Two-phased sampling mechanism: 100% inclusion rate if HIV-1 positive in week 28; based on matching otherwise.

- Baseline covariates($L$): sex, age, BMI, behavioral HIV risk.
- Intervention(s) ($A$): post-vaccination T-cell activity markers.
- Outcome ($Y$): HIV-1 infection status at week 28 of tiral.
- 12-color intracellular cytokine staining (ICS) assay.
- Cryopreserved peripheral blood mononuclear cells were stimulated with synthetic HIV-1 peptide pools.
- All immune responses are assayed *after* the endpoints of interest (HIV-1 infection status) are collected.
- **Conclusion:** Understanding which immune responses impact vaccine efficacy helps develop more efficacious vaccines.
- A vaccine effective at preventing HIV-1 acquisition would be a cost-effective and durable approach to halting the worldwide epidemic.

## Two-phase sampling censors the complete data structure

- Complete (unobserved) data $X = (L, A, S, Y) \sim P_0^X \in \mathcal{M}^X$, as per the full HVTN 505 trial cohort (Hammer et al. 2013):
  - $L$ (baseline covariates): sex, age, BMI, behavioral HIV risk,
  - $A$ (treatment): vaccination status (randomized),
  - $S$ (exposure): immune response profile for CD4+ and CD8+,
  - $Y$ (outcome of interest): HIV-1 infection status at week 28.
- Observed data $O = (C, CX) = (L, C, CS, Y)$.
  - $C \in \{0, 1\}$ indicates inclusion in the second-phase sample.
  - Implicitly conditioning on the vaccine arm, i.e., $O = X \mid A = 1$.

- $P_0^X$ — true (unknown) distribution of the full data $X$,
- $\mathcal{M}_{NP}^X$ — nonparametric statistical model.

## NPSEM with static interventions

- Use a nonparametric structural equation model (NPSEM) to describe the generation of $X$ (Pearl 2009), specifically

$$L = f_L(U_L); S = f_S(L, U_S); Y = f_Y(S, L, U_Y)$$

- Implies a model for the distribution of counterfactual random variables generated by interventions on the process.
- A *static intervention* replaces $f_S$ with a specific value $s$ in its conditional support $S \mid A = 1, L$.
- This requires specifying a particular value of the exposure under which to evaluate the outcome *a priori*.

## NPSEM with stochastic interventions

- *Stochastic interventions* modify the value $S$ would naturally assume by drawing from a modified exposure distribution.
- Consider the post-intervention value $S^\star \sim G^\star(\cdot \mid L)$; static interventions are a special case (degenerate distribution).
- Such an intervention generates a counterfactual random variable $Y_{G^\star} := f_Y(S^\star, L, U_Y)$, with distribution $P_0^\delta$, .
- We aim to estimate $\psi_{0,\delta} := \mathbb{E}_{P_0^\delta}\{Y_{G^\star}\}$, the counterfactual mean under the post-intervention exposure distribution $G^\star$.

## Stochastic interventions for the causal effects of shifts

- Díaz and van der Laan (2012; 2018)'s *stochastic* interventions

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

- Our estimand is $\psi_{0,d} := \mathbb{E}_{P_0^d}\{Y_{d(S,L)}\}$, mean of $Y_{d(S,L)}$.
- Statistical target parameter is $\Psi(P_0^X) = \mathbb{E}_{P_0^X}\overline{Q}(d(S, L), L)$, counterfactual mean of the *shifted* outcome mechanism.
- For HVTN 505, $\psi_{0,d}$ is the counterfactual risk of HIV-1 infection, had the observed value of the immune response been altered under the rule $d(S, L)$ defining $G^{\star}(\cdot \mid L)$.

- Causal estimand: counterfactual mean of HIV-1 infection (risk) under a *shifted* immunogenic response distribution.

## 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 (Rubin 1978; 1980)*
- $Y_i^{d(s_i,l_i)} = Y_i$ *in the event* $S_i = d(s_i, l_i)$*, for* $i = 1, \ldots, n$

**Assumption 2: *Ignorability***

$S_i \perp\!\!\!\perp Y_i^{d(s_i,l_i)} \mid L_i$*, for* $i = 1, \ldots, n$

**Assumption 3: *Positivity***

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

- This positivity assumption is not quite the same as that required for categorical interventions.
- In particular, we do not require that the intervention density place mass across all strata defined by $L$.
- Rather, we merely require the post-intervention quantity be seen in the observed data for given $s_i \in \mathcal{S}$ and $l_i \in \mathcal{L}$.

## Literature: Díaz and van der Laan (2012)

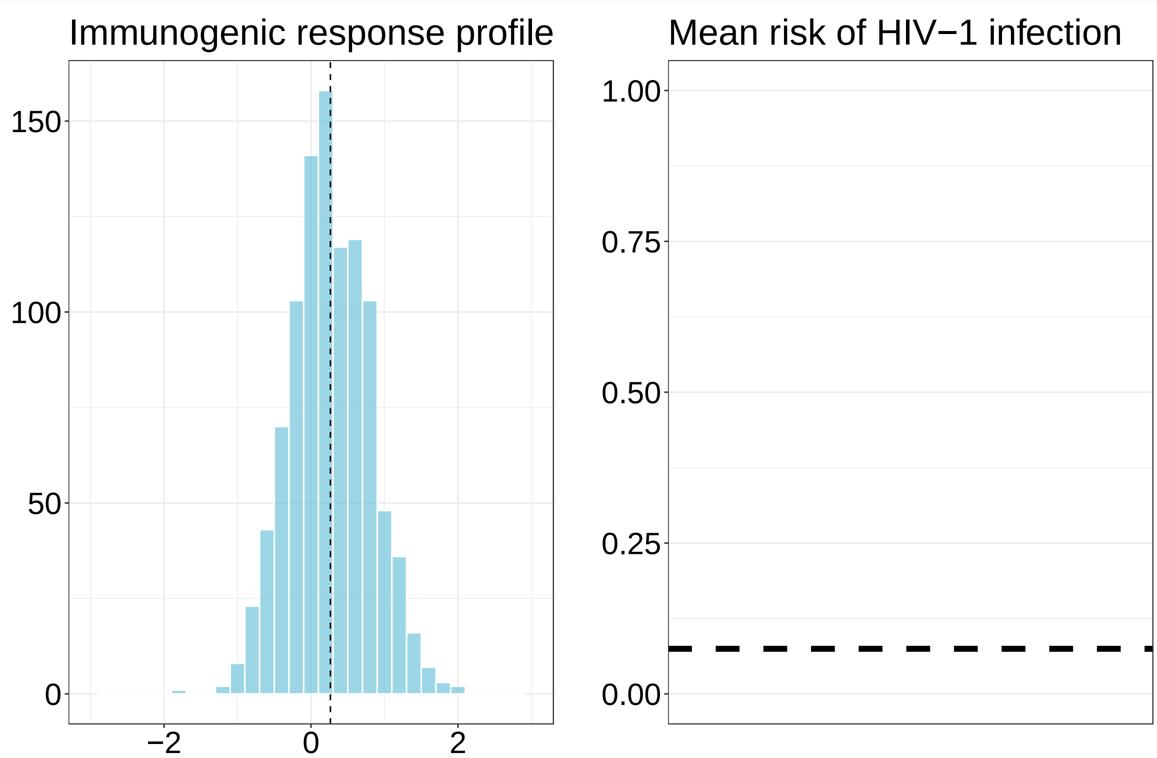
- *Proposal:* Evaluate outcome under an altered *intervention distribution* — e.g., $P_{\delta}(g_0)(S = s \mid L) = g_0(s - \delta(L) \mid L)$.
- Identification conditions for a statistical parameter of the counterfactual outcome $\psi_{0,d}$ under such an intervention.
- Show that the causal quantity of interest $\mathbb{E}_0\{Y_{d(S,L)}\}$ is identified by a functional of the distribution of $X$:

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

- Provides a derivation based on the efficient influence function (EIF) with respect to the nonparametric model $\mathcal{M}$.

- The identification result allows us to write down the causal quantity of interest in terms of a functional of the observed data.
- Key innovation: loosening standard assumptions through a change in the observed intervention mechanism.
- Problem: globally altering an intervention mechanism does not necessarily respect individual characteristics.
- The authors build IPW, one-step, and TML estimators, comparing the three different approaches.

## HIV-1 risk under shifted immunogenic responses



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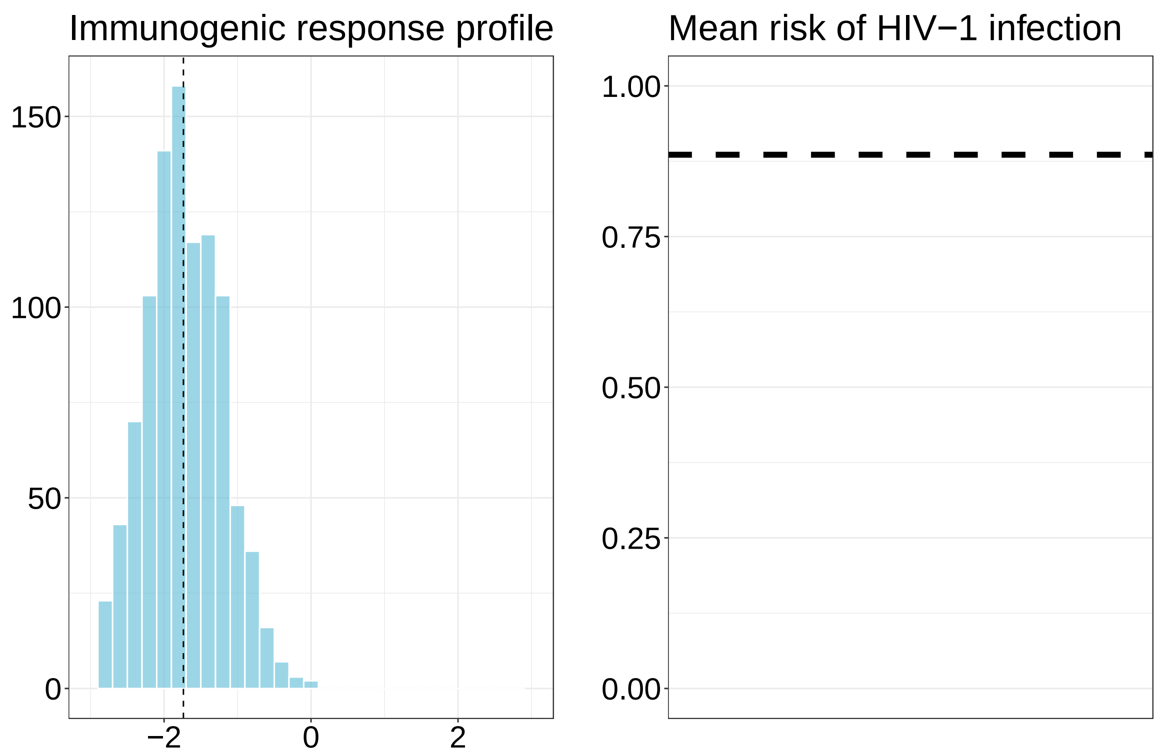

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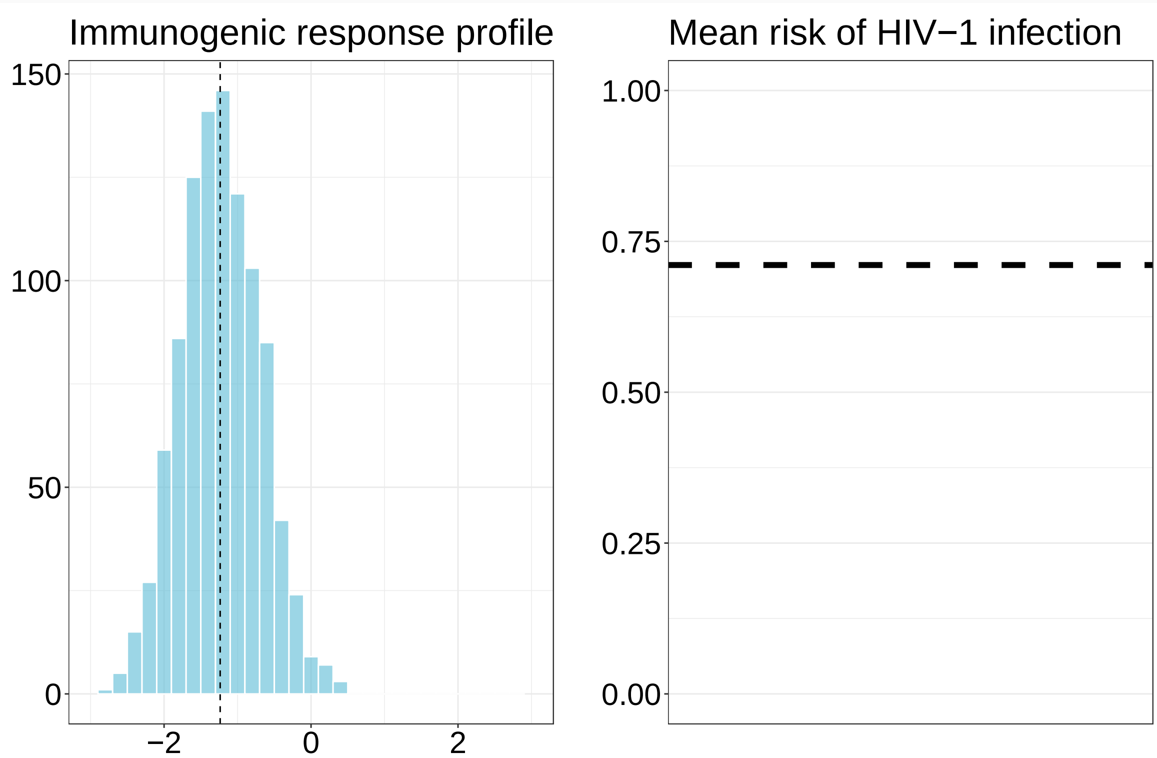

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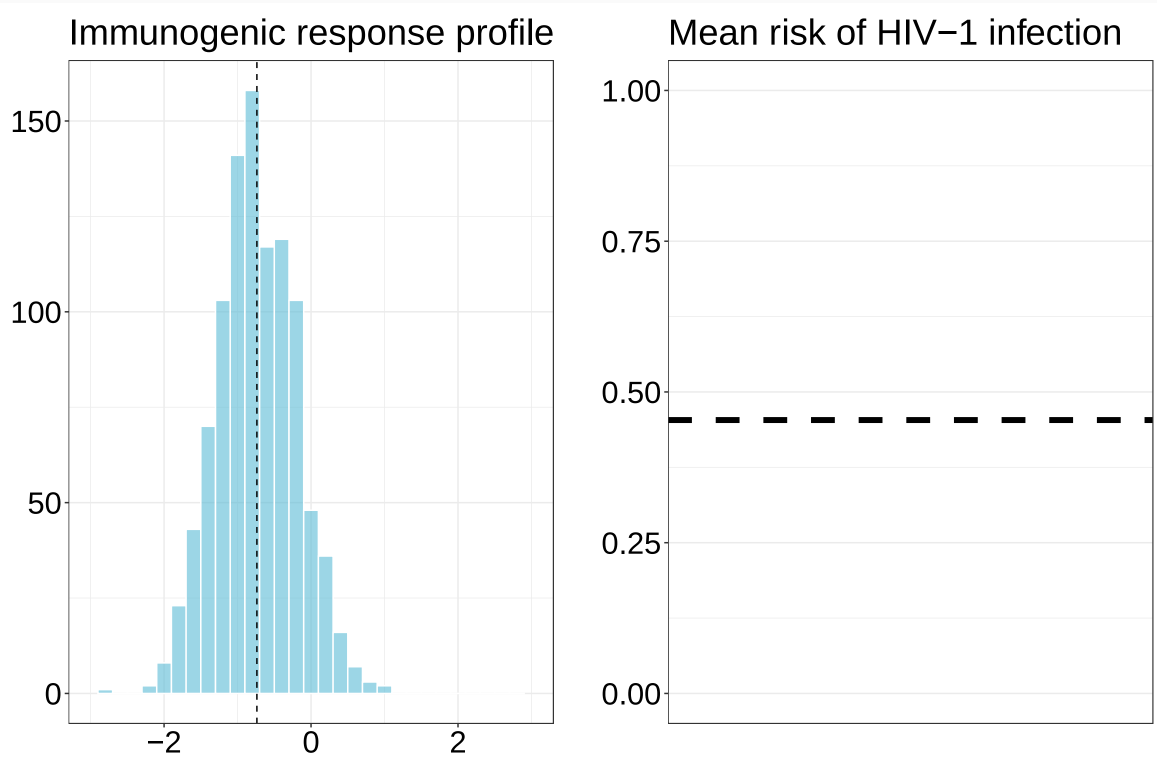

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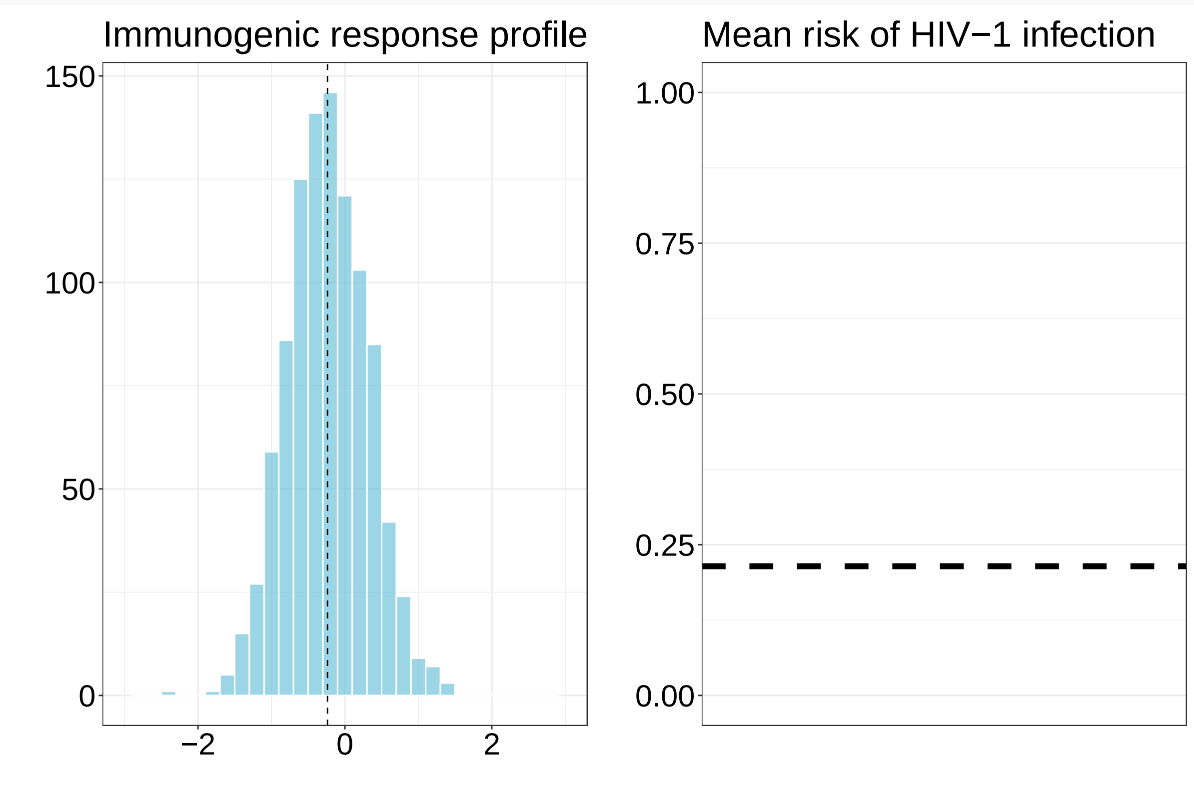

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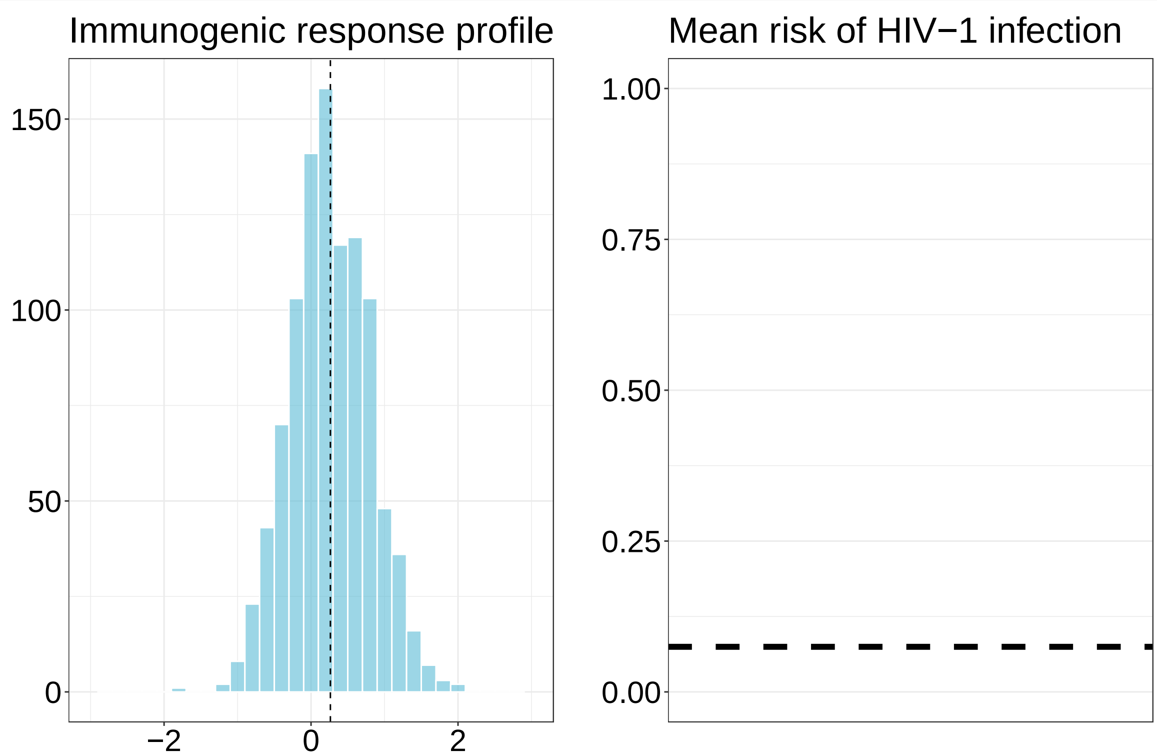

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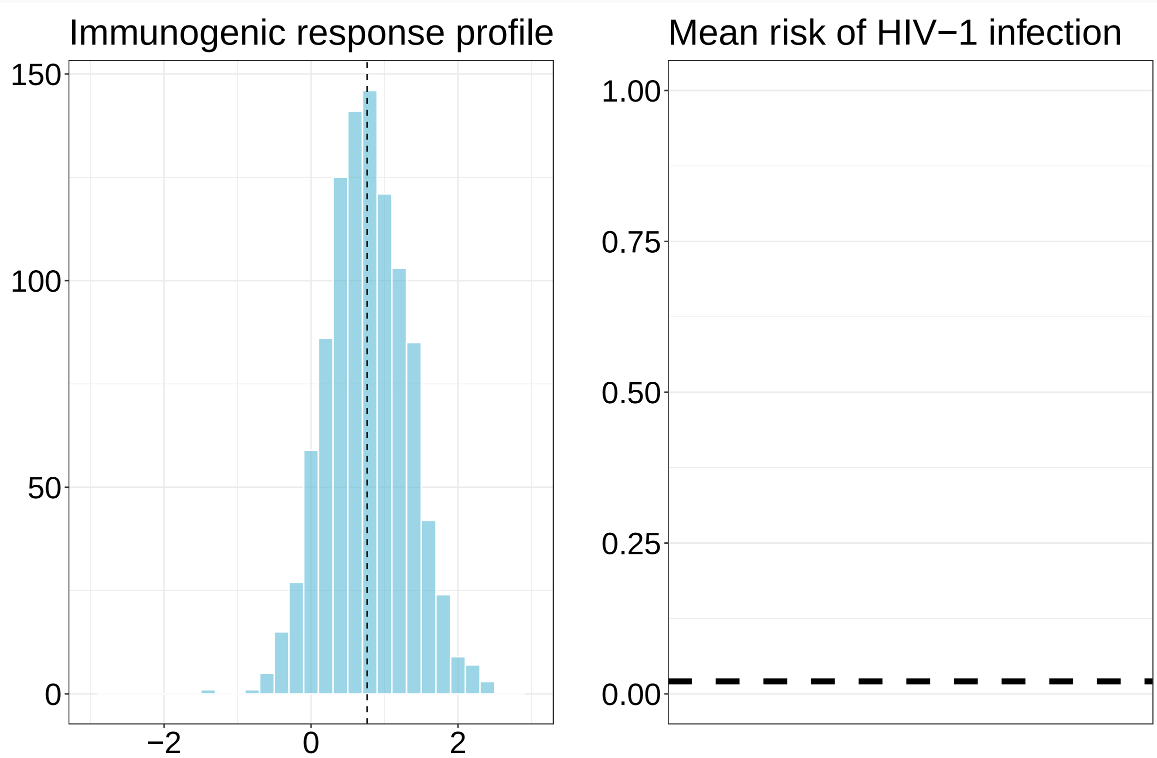

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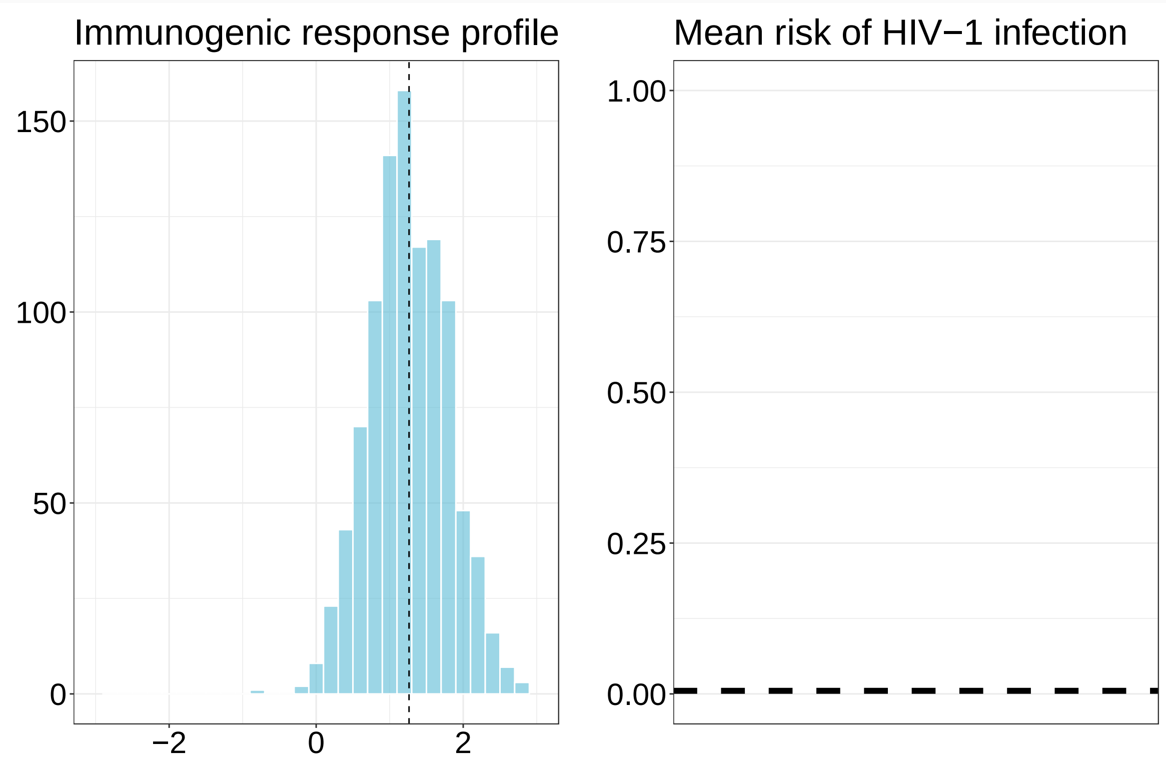

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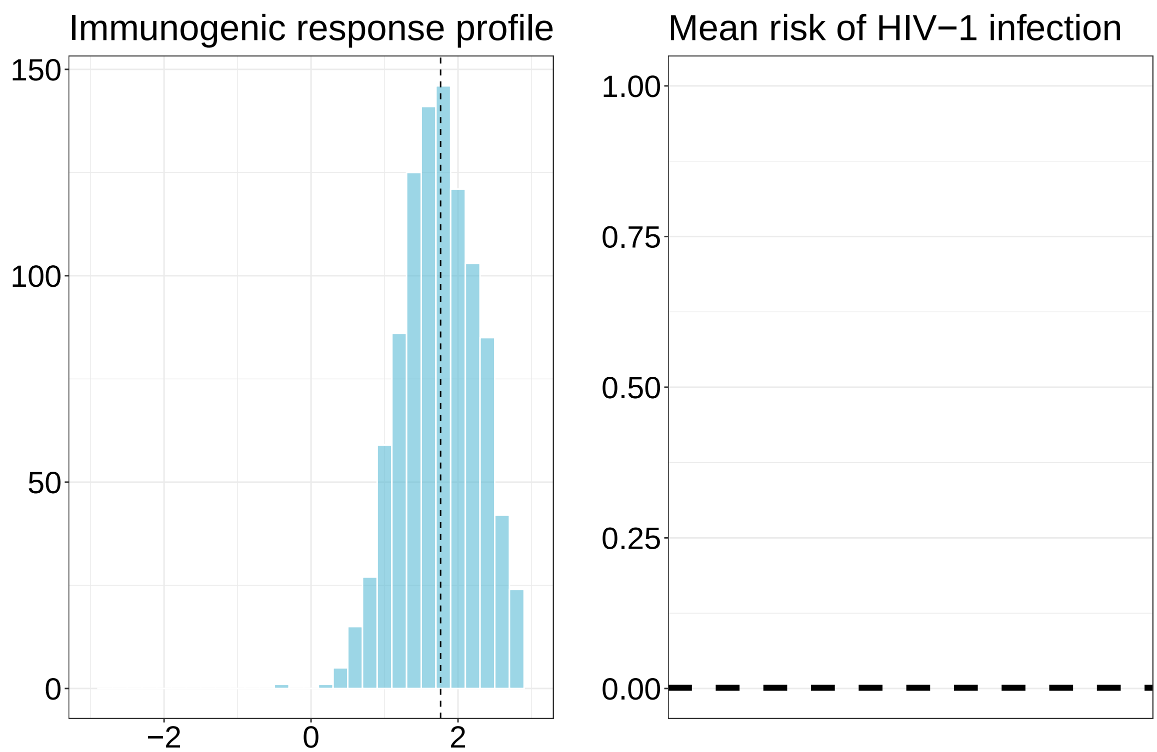

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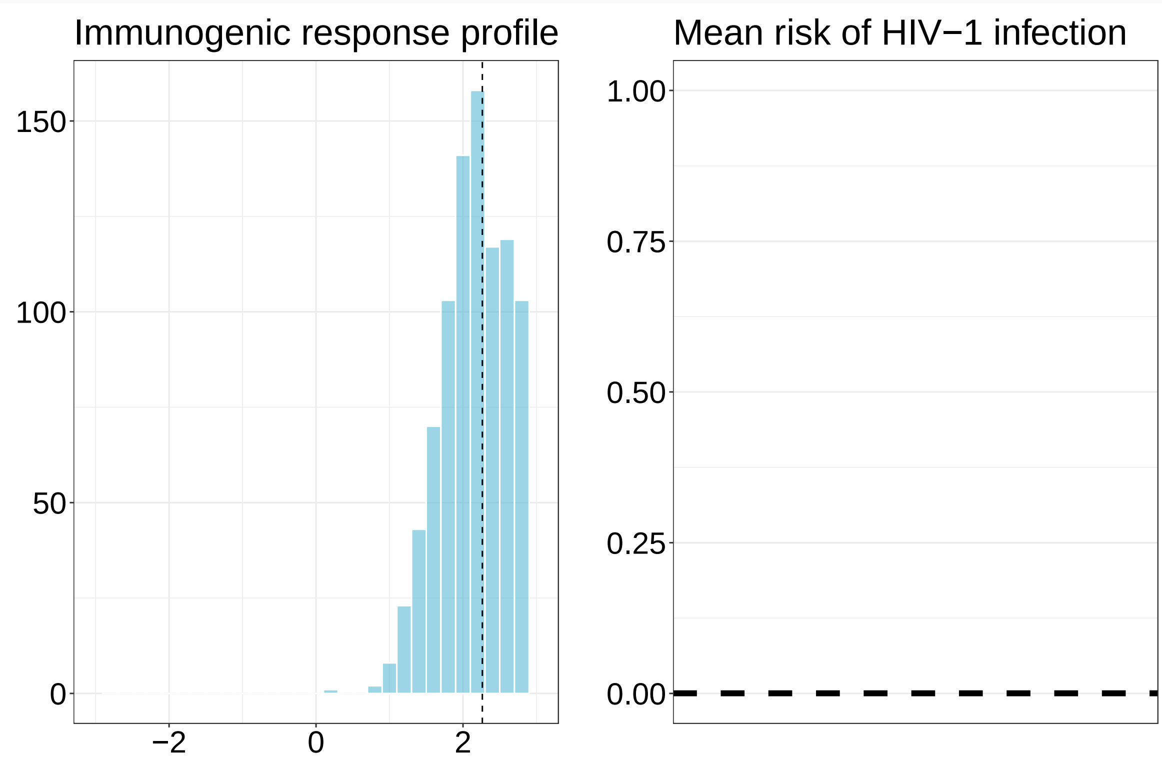

## Flexible, efficient estimation

- The efficient influence function (EIF) is:

$$D(P_0^X)(x) = H(s,l)(y - \overline{Q}(s,l)) + \overline{Q}(d(s,l),l) - \Psi(P_0^X).$$

- The one-step estimator corrects bias by adding the empirical mean of the estimated EIF to the substitution estimator:

$$\Psi_n^+ = \frac{1}{n}\sum_{i=1}^{n} \overline{Q}_n(d(S_i,L_i),L_i) + D_n(O_i).$$

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

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

- Both estimators are doubly robust.

- Both estimators are CAN even when nuisance parameters are estimated via flexible, machine learning techniques.
- Semiparametric-efficient estimation thru solving efficient influence function estimating equation wrt the model $\mathcal{M}$.
- The auxiliary covariate simplifies when the treatment is in the limits (conditional on $W$) — i.e., for $S_i \in (u(l) - \delta, u(l))$, then we have $H(s, l) = \frac{g_0(s-\delta|l)}{g_0(s|l)} + 1$.
- Need to explicitly remind the audience what $u(l)$ is again. It's only appeared once at this point, and only been mentioned in passing.

## Augmented estimators for two-phase sampling designs

- Rose and van der Laan (2011) introduce the IPCW-TMLE, to be used when observed data is subject to two-phase sampling.
- *Initial proposal:* correct for two-phase sampling by using a loss function with inverse probability of censoring weights:

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

- When the sampling mechanism $\pi_0(Y, L)$ can be estimated by a parametric form, this procedure yields an efficient estimator.
- However, when machine learning is used (e.g., when $\pi_0(Y, L)$ is not *known by design*), this is insufficient.

## Efficient estimation and multiple robustness

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

$$D(P_0^X)(o) = \frac{c}{\pi_0(y,l)} D^F(P_0^X)(x) - \left(1 - \frac{c}{\pi_0(y,l)}\right) \cdot \mathbb{E}(D^F(P_0^X)(x) \mid C = 1, Y = y, L = l),$$

  - Expresses observed data EIF $D^F(P_0^X)(o)$ in terms of full data EIF $D^F(P_0^X)(x)$; inclusion of second term ensures efficiency.
  - The expectation of the full data EIF $D^F(P_0^X)(x)$, taken only over units selected by the sampling mechanism (i.e., $C = 1$).
- A unique multiple robustness property — combinations of $(g_0(L), \overline{Q}_0(S,L)) \times (\pi_0(Y,L), \mathbb{E}(D^F(P_0^X)(x) \mid C = 1, Y, L))$.

## Fighting the HIV-1 epidemic with preventive vaccines

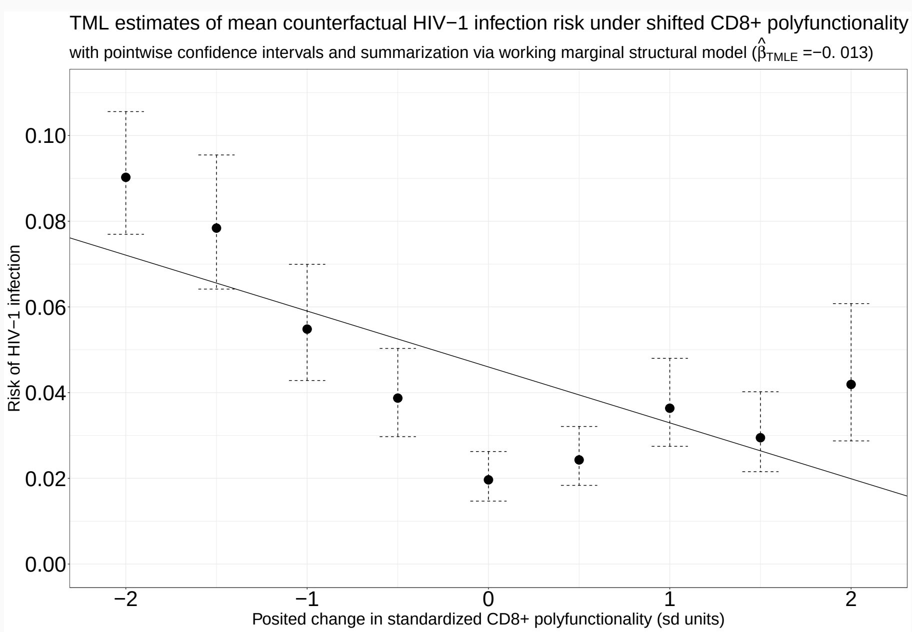


**Figure 1:** Analysis of HIV-1 risk as a function of CD8+ immunogenicity, using `R` package `txshift` (`https://github.com/nhejazi/txshift`).

## Big picture takeaways

- Vaccine efficacy evaluation helps to develop enhanced vaccines better informed by biological properties of the target disease.
- HIV-1 vaccines modulate immunogenic response profiles as part of their mechanism for lowering HIV-1 infection risk.
- *Stochastic* interventions constitute a flexible framework for considering **realistic** treatment/intervention policies.
- Large-scale (vaccine) trials often use two-phase designs — need to (carefully!) accommodate for sampling complications.
- We've developed robust, open source statistical software for assessing stochastic interventions in observational studies.

## Thank you!

https://nimahejazi.org

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https://github.com/nhejazi

https://doi.org/10.1111/biom.13375

# At Warp Speed – COVID-19 Vaccine Trials

## COVID-19 Vaccine Development

- *Nucleic acid vaccines*: Moderna (mRNA), Pfizer (mRNA)
- *Viral-vectored vaccines*: AstraZeneca (chimpanzee adenovirus), Janssen (human adenovirus)
- *Subunit vaccines*: NovaVax, Sanofi / GlaxoSmithKline
- *Weakened/inactivated vaccines*: Sinopharm, Sinovac

- Nucleic acid vaccines have never been approved before, but are quick to manufacture.
- Viral-vectored vaccines are also quick to manufacture but can develop immunity against vector.
- Subunit vaccines are a construct of several effective vaccines, but are slower to manufacture and often require an adjuvant.

## Operation Warp Speed (OWS)

- Do we have the time? Polio (7 years), Measles (9 years), Chickenpox (34 years), Mumps (4 years), HPV (15 years).
- OWS: "300M doses of safe, effective vaccine by 01 Jan. 2021".
- How? Typical process timeline (73 months) replaced by an *accelerated* process of 14 months.
- COVID-19 Prevention Network (CoVPN):
  - formed by NIAID to establish a unified clinical trial network for evaluating vaccines and monoclonal antibodies.
  - Statisticians: primary trial design/analysis, sequential efficacy monitoring, safety monitoring, immune correlates.

## 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.

## Measuring Correlates: Two-Phase Designs

- Running assays on $> 30,000$ blood draws is timely, expensive, and, as it turns out, statistically unnecessary.
- Instead we measure immune responses via a case-cohort design (Prentice 1986):
  - a stratified random subcohort ($\approx$ 1600 individuals)
  - all SARS-CoV-2 and COVID endpoints.
- Case-cohort designs are a special case of two-phase sampling (Breslow et al. 2003; 2009):
  - Phase 1: measure baseline, vaccine, endpoint on everyone.
  - Phase 2: given baseline, vaccine, endpoint, select members of immune response subcohort with (possibly known) probability.

## Stochastic–Interventional Vaccine Efficacy

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

$$\text{SVE}(\delta) = 1 - \frac{\mathbb{E}[\mathbb{P}(Y = 1 \mid A = 1, S = s + \delta, L = l) \mid A = 1, L]}{\mathbb{P}(Y(0) = 1)}.$$

- $\mathbb{P}(Y(0) = 1)$: counterfactual infection risk in the placebo arm — under randomization, $\mathbb{P}(Y(0) = 1) = \mathbb{P}(Y = 1 \mid A = 0)$.
- Summarizes VE thru stochastic interventions indexed by $\delta$.
- Further details in CoVPN's public immune correlates SAP at `https://doi.org/10.6084/m9.figshare.13198595`.

## Additional Complexities of Two-Phase Designs

- Observed data structure: $O = (L, A, Z, CS, Y, C)$
  - $A \in \{0, 1\}$: randomized vaccination assignment
  - $Z$: post-vaccination confounder (e.g., unblinded risky behavior)
  - $S$: candidate mCoPs (causal mediators)
  - $Y$: symptomatic SARS-CoV-2 infection
  - $C := f(Y, L)$: selection into second-phase sample
- But what about $O = (L, A, Z, CS, \Delta, \widetilde{T}, C)$?
  - $\widetilde{T} = \min(T_F, T_C)$: possibly right-censored time to infection
  - $\Delta = \mathbb{I}(T_F < T_C)$: symptomatic SARS-CoV-2 infection
  - Can $C$ still be a function of $\widetilde{T}$?

- Goal: assess *indirect* effect of vaccination through mCoPs.
- Define/identify new mCoPs to be used as surrogate endpoints.
- Could also have missing outcome in the binary endpoint case.

## Causal Mediation Analysis: Explanation and Mechanism

- Identification assumptions:
  - A1: No unmeasured confounding of $\{A, Y\}$ relationship.
  - A2: No unmeasured confounding of $\{S, Y\}$ relationship.
  - A3: No unmeasured confounding of $\{A, S\}$ relationship.
  - A4: No $\{S, Y\}$ confounder affected by $A$, i.e., no $Z$.
- *Indirect* effects: thru pathways involving candidate mCoPs.
  - Natural (in)direct effects (Robins and Greenland 1992, Pearl 2013): binary $A$ and $S$, no $Z$, "cross-world" independence.
  - Stochastic (in)direct effects (Díaz and Hejazi 2020): continuous $A$ and $S$, no $Z$; no "cross-world" exclusion.
  - Interventional (in)direct effects (Díaz et al. 2020): binary $A$, continuous $S$, $Z$ OK, no "cross-world" exclusion.
  - Stochastic interventional (in)direct effects (Hejazi et al. 2020): continuous $A$ and $S$, $Z$ ok, no "cross-world" exclusion.

- A1, A3 hold in randomized trials.
- A2 may not hold: include all mutual $\{S, Y\}$ predictors, then perform sensitivity analysis.
- A4 usually doesn't hold: either measure $S$ right after $A$ or develop more flexible effect definitions.
- "Cross-world" independence: $Y(a, s) \perp S(a') \quad \forall s$; untestable in RCTs
- Extensions for two-phase sampling?

# Appendix

## Literature: Haneuse and Rotnitzky (2013)

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

$$g_{0,\delta}(s \mid l) = \sum_{j=1}^{J(l)} I_{\delta,j}\{h_j(s,l), l\} g_0\{h_j(s,l) \mid l\} h_j^{'}(s,l)$$

- Such intervention policies account for the natural value of the intervention $S$ directly yet are interpretable as the imposition of an altered intervention mechanism.
- Identification conditions for assessing the parameter of interest under such interventions appear technically complex (at first).

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- Shifts of the form $d(S, L)$ are considerably more interesting since these are realistic intervention policies.
- Example: consider an individual with an extremely high immune response but whose baseline covariates $L$ suggest we shift the response still higher. Such a shift may not be biologically plausible (impossible, even) but we cannot account for this if the shift is only a function of $L$.
- The authors build IPW, outcome regression, and non-iterative doubly robust estimators, as well as an approach based on MSMs.
- Piecewise smooth invertibility: This assumption ensures that we can use the change of variable formula when computing integrals over $S$ and it is useful to study the estimators that we propose in this paper.

## Literature: Young et al. (2014)

- Establishes equivalence between g-formula when proposed intervention depends on natural value and when it does not.
- This equivalence leads to a sufficient positivity condition for estimating the counterfactual mean under MTPs via the same statistical functional studied in Díaz and van der Laan (2012).
- Extends earlier identification results, providing a way to use the same statistical functional to assess $\mathbb{E}Y_{d(S,L)}$ or $\mathbb{E}Y_{d(L)}$.
- The authors also consider limits on implementing shifts $d(S, L)$, and address working in a longitudinal setting.

## Literature: Díaz and van der Laan (2018)

- Builds on the original proposal, accomodating MTP-type shifts $d(S, L)$ proposed after their earlier work.
- To protect against positivity violations, considers a specific shifting mechanism:

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

- Proposes an improved TMLE algorithm, with a single auxiliary covariate for constructing the TML estimator.

## Nonparametric conditional density estimation

- To compute the auxiliary covariate $H(s, l)$, we need to estimate conditional densities $g(S \mid L)$ and $g(S - \delta \mid L)$.
- There is a rich literature on density estimation, we follow the approach proposed in Díaz and van der Laan (2011).
- To build a conditional density estimator, consider

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

  for $\alpha_{t-1} \leq s < \alpha_t$.

  - This is a classification problem, where we estimate the probability that a value of $S$ falls in a bin $[\alpha_{t-1}, \alpha_t)$.
  - The choice of the tuning parameter $t$ corresponds roughly to the choice of bandwidth in classical kernel density estimation.

## Nonparametric conditional density estimation

- Díaz and van der Laan (2011) propose a reformulation of this classification approach as a set of hazard regressions.
- To effectively employ this proposed reformulation, consider

$$\mathbb{P}(S \in [\alpha_{t-1}, \alpha_t) \mid L) = \mathbb{P}(S \in [\alpha_{t-1}, \alpha_t) \mid S \geq \alpha_{t-1}, L) \times \prod_{j=1}^{t-1} \{1 - \mathbb{P}(S \in [\alpha_{j-1}, \alpha_j) \mid S \geq \alpha_{j-1}, L)\}$$

  - The likelihood of this model may be expressed to correspond to the likelihood of a binary variable in a data set expressed via a long-form repeated measures structure.
  - Specifically, the observation of $X_i$ is repeated as many times as intervals $[\alpha_{t-1}, \alpha_t)$ are before the interval to which $S_i$ belongs, and the binary variables indicating $S_i \in [\alpha_{t-1}, \alpha_t)$ are recorded.

## Density estimation with the Super Learner algorithm

- To estimate $g(S \mid L)$ and $g(S - \delta \mid L)$, use a pooled hazard regression, spanning the support of $S$.
- We rely on the Super Learner algorithm of van der Laan et al. (2007) to build an ensemble learner that optimally weights each of the proposed regressions, using cross-validation (CV).
- The Super Learner algorithm uses $V$-fold CV to train each proposed regression model, weighting each by the inverse of its average risk across all $V$ holdout sets.
- By using a library of regression estimators, we invoke the result of van der Laan et al. (2004), who prove this likelihood-based cross-validated estimator to be asymptotically optimal.

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- The auxiliary covariate simplifies when the treatment is in the limits (conditional on $L$) — i.e., for $S_i \in (u(l) - \delta, u(l))$, then we have $H(s, l) = \frac{g_0(s-\delta|l)}{g_0(s|l)} + 1$.
- Asymptotically optimal in the sense that it performs as well as the oracle selector as the sample size increases.

## Key properties of TML estimators

- **Asymptotic linearity:**

$$\Psi(P_n^\star) - \Psi(P_0^X) = \frac{1}{n}\sum_{i=1}^{n} D(P_0^X)(X_i) + o_P\left(\frac{1}{\sqrt{n}}\right)$$

- **Gaussian limiting distribution:**

$$\sqrt{n}(\Psi(P_n^\star) - \Psi(P_0^X)) \to N(0, Var(D(P_0^X)(X)))$$

- **Statistical inference:**

$$\text{Wald-type confidence interval} : \Psi(P_n^\star) \pm z_{1-\frac{\alpha}{2}} \cdot \frac{\sigma_n}{\sqrt{n}},$$

where $\sigma_n^2$ is computed directly via $\sigma_n^2 = \frac{1}{n}\sum_{i=1}^{n} D^2(\cdot)(X_i)$.

Under the additional condition that the remainder term $R(\hat{P}^\star, P_0)$ decays as $o_P\left(\frac{1}{\sqrt{n}}\right)$, we have that $\Psi_n - \Psi_0 = (P_n - P_0)\cdot D(P_0) + o_P\left(\frac{1}{\sqrt{n}}\right)$, which, by a central limit theorem, establishes a Gaussian limiting distribution for the estimator, with variance $V(D(P_0))$, the variance of the efficient influence function when $\Psi$ admits an asymptotically linear representation.
The above implies that $\Psi_n$ is a $\sqrt{n}$-consistent estimator of $\Psi$, that it is asymptotically normal (as given above), and that it is locally efficient. This allows us to build Wald-type confidence intervals, where $\sigma_n^2$ is an estimator of $V(D(P_0))$. The estimator $\sigma_n^2$ may be obtained using the bootstrap or computed directly via $\sigma_n^2 = \frac{1}{n}\sum_{i=1}^{n} D^2(\bar{Q}_n^\star, g_n)(O_i)$
We obtain semiparametric-efficient estimation and robust inference in the nonparametric model $\mathcal{M}$ by solving the efficient influence function.

1. If $D(\bar{Q}_n^\star, g_n)$ converges to $D(P_0)$ in $L_2(P_0)$ norm.
2. The size of the class of functions $\bar{Q}_n^\star$ and $g_n$ is bounded (technically, $\exists \mathcal{F}$ s.t. $D(\bar{Q}_n^\star, g_n) \in \mathcal{F}$ w.h.p., where $\mathcal{F}$ is a Donsker class)

## 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 $\epsilon$ 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 $\Psi_n$ of the target parameter, defining update $\overline{Q}_n^{\star}$ of the initial estimate $\overline{Q}_{n,\epsilon_n}$:
$$\Psi_n = \Psi(P_n^{\star}) = \frac{1}{n}\sum_{i=1}^{n} \overline{Q}_n^{\star}(d(S_i, L_i), L_i).$$

- We recommend using nonparametric methods for the initial estimators, as consistent estimation is necessary for efficiency of the estimator $\Psi_n$.
- Intuition for the submodel fluctuation?

## 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 $\Psi_n$ 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 TML estimate in each iteration, until $\frac{1}{n}\sum_{i=1}^{n} \text{EIF}_i < \frac{1}{n}$.

- We recommend using nonparametric methods for the initial estimators, as consistent estimation is necessary for efficiency of the estimator $\Psi_n$.
- Intuition for the submodel fluctuation?
- This process includes the use of HAL to fit the regression of the EIF contributions on the sampling node $\{Y, L\}$.

# Identifying the best efficient estimator

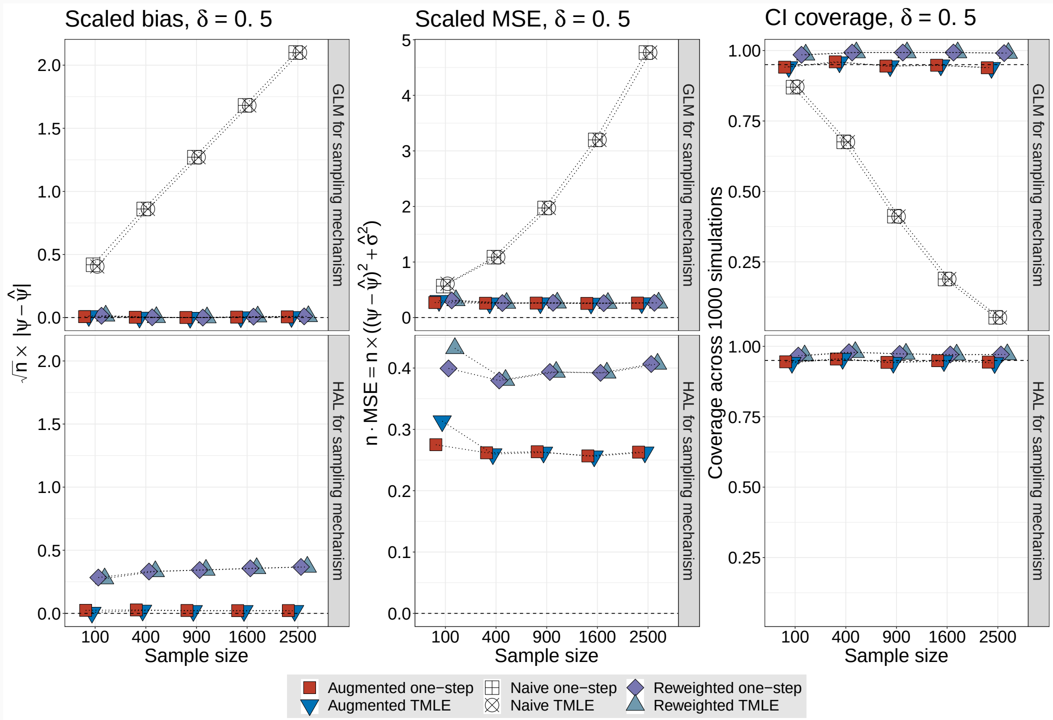


**Figure 2:** Relative performance of reweighted and augmented estimators.

## A linear modeling perspective

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

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

- Thus, a *unit shift* in $S$ (i.e., $\delta = 1$) may be seen as inducing a change in the difference in outcomes of magnitude $\beta_1$.

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- We extend this result to the mean counterfactual outcomes under the nonparametric model $\mathcal{M}$.

## A causal inference perspective

- Consider a data structure: $(Y_s, s \in \mathcal{S})$.
- To posit a linear model, let $Y_s = \beta_0 + \beta_1 s + \epsilon_s$ for $s \in \mathcal{S}$, 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, $Y_{s'+\delta} - Y_{s'}$, for some $s' \in \mathcal{S}$, may be expressed

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

- Thus, a *unit shift* for $s' \in S$ (i.e., $\delta = 1$) may be seen as inducing a change in the difference in the counterfactual outcomes of magnitude $\beta_1$.

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- Note that this analysis is exactly what we're told we **cannot** do in "linear models 101" — that is, the slope of a regression line cannot be interpreted as *causing* a change in the outcome.
- We extend this result to the mean counterfactual outcomes under the nonparametric model $\mathcal{M}$.

## Slope in a semiparametric model

- Consider the stochastic intervention $g^{\star}(\cdot \mid L)$:

$$\mathbb{E}Y_{g^{\star}} = \int_L \int_s \mathbb{E}(Y \mid S = s, L) g(s - \delta \mid L) \cdot ds \cdot dP_0(L)$$
$$= \int_L \int_z \mathbb{E}(Y \mid S = z + \delta, L) g(z \mid L) \cdot dz \cdot dP_0(L),$$

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

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

$$\mathbb{E}Y_{g^{\star}} - \mathbb{E}Y = \int_L \int_z [\mathbb{E}(Y \mid S = z + \delta, L) - \mathbb{E}(Y \mid S = z, L)] \, g(z \mid L) \cdot dz \cdot dP_0(L)$$
$$= [\beta(z + \delta) + \theta(L)] - [\beta z + \theta(L)]$$
$$= \beta\delta$$

## References


Breiman, L. (1996). Stacked regressions. *Machine Learning*, 24(1):49–64.

Breslow, N., McNeney, B., Wellner, J. A., et al. (2003). Large sample theory for semiparametric regression models with two-phase, outcome dependent sampling. *The Annals of Statistics*, 31(4):1110–1139.

Breslow, N. E., Lumley, T., Ballantyne, C. M., Chambless, L. E., and Kulich, M. (2009). Improved horvitz–thompson estimation of model parameters from two-phase stratified samples: applications in epidemiology. *Statistics in Biosciences*, 1(1):32–49.

Díaz, I. and Hejazi, N. S. (2020). Causal mediation analysis for stochastic interventions. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 82(3):661–683.

Díaz, I., Hejazi, N. S., Rudolph, K. E., and van der Laan, M. J. (2020). Non-parametric efficient causal mediation with intermediate confounders. *Biometrika*.

Díaz, I. and van der Laan, M. J. (2011). Super learner based conditional density estimation with application to marginal structural models. *The international journal of biostatistics*, 7(1):1–20.

Díaz, I. and van der Laan, M. J. (2012). Population intervention causal effects based on stochastic interventions. *Biometrics*, 68(2):541–549.

Díaz, I. and van der Laan, M. J. (2018). Stochastic treatment regimes. In *Targeted Learning in Data Science: Causal Inference for Complex Longitudinal Studies*, pages 167–180. Springer Science & Business Media.

Dudoit, S. and van der Laan, M. J. (2005). Asymptotics of cross-validated risk estimation in estimator selection and performance assessment. *Statistical Methodology*, 2(2):131–154.

Hammer, S. M., Sobieszczyk, M. E., Janes, H., Karuna, S. T., Mulligan, M. J., Grove, D., Koblin, B. A., Buchbinder, S. P., Keefer, M. C., Tomaras, G. D., et al. (2013). Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. *New England Journal of Medicine*, 369(22):2083–2092.

Haneuse, S. and Rotnitzky, A. (2013). Estimation of the effect of interventions that modify the received treatment. *Statistics in medicine*, 32(30):5260–5277.

Hejazi, N. S., Rudolph, K. E., van der Laan, M. J., and Díaz, I. (2020). Nonparametric causal mediation analysis for stochastic interventional (in)direct effects. under review at *Journal of the American Statistical Association (Theory & Methods)*.

Holland, P. W. (1986). Statistics and causal inference. *Journal of the American statistical Association*, 81(396):945–960.

Janes, H. E., Cohen, K. W., Frahm, N., De Rosa, S. C., Sanchez, B., Hural, J., Magaret, C. A., Karuna, S., Bentley, C., Gottardo, R., et al. (2017). Higher t-cell responses induced by dna/rad5 hiv-1 preventive vaccine are associated with lower hiv-1 infection risk in an efficacy trial. *The Journal of infectious diseases*, 215(9):1376–1385.

Kennedy, E. H. (2018). Nonparametric causal effects based on incremental propensity score interventions. *Journal of the American Statistical Association*, (just-accepted).

Kennedy, E. H., Ma, Z., McHugh, M. D., and Small, D. S. (2017). Non-parametric methods for doubly robust estimation of continuous treatment effects. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 79(4):1229–1245.

Pearl, J. (2009). *Causality: Models, Reasoning, and Inference*. Cambridge University Press.

Pearl, J. (2013). Direct and indirect effects. *arXiv preprint arXiv:1301.2300*.

Plotkin, S. A. and Gilbert, P. B. (2012). Nomenclature for immune correlates of protection after vaccination. *Clinical Infectious Diseases*, 54(11):1615–1617.

Prentice, R. L. (1986). A case-cohort design for epidemiologic cohort studies and disease prevention trials. *Biometrika*, 73(1):1–11.

Prentice, R. L. (1989). Surrogate endpoints in clinical trials: definition and operational criteria. *Statistics in medicine*, 8(4):431–440.

Price, B. L., Gilbert, P. B., and van der Laan, M. J. (2018). Estimation of the optimal surrogate based on a randomized trial. *Biometrics*, 74(4):1271–1281.

Robins, J. M. and Greenland, S. (1992). Identifiability and exchangeability for direct and indirect effects. *Epidemiology*, pages 143–155.

Rose, S. and van der Laan, M. J. (2011). A targeted maximum likelihood estimator for two-stage designs. *The International Journal of Biostatistics*, 7(1):1–21.

Rosenbaum, P. R. and Rubin, D. B. (1983). The central role of the propensity score in observational studies for causal effects. *Biometrika*, 70(1):41–55.

Rubin, D. B. (1978). Bayesian inference for causal effects: The role of randomization. *The Annals of statistics*, pages 34–58.

Rubin, D. B. (1980). Randomization analysis of experimental data: The fisher randomization test comment. *Journal of the American Statistical Association*, 75(371):591–593.

Rubin, D. B. (2005). Causal inference using potential outcomes: Design, modeling, decisions. *Journal of the American Statistical Association*, 100(469):322–331.

van der Laan, M. J., Dudoit, S., and Keles, S. (2004). Asymptotic optimality of likelihood-based cross-validation. *Statistical Applications in Genetics and Molecular Biology*, 3(1):1–23.

van der Laan, M. J., Polley, E. C., and Hubbard, A. E. (2007). Super Learner. *Statistical Applications in Genetics and Molecular Biology*, 6(1).

van der Laan, M. J. and Rubin, D. (2006). Targeted maximum likelihood learning. *The International Journal of Biostatistics*, 2(1).

Wolpert, D. H. (1992). Stacked generalization. *Neural networks*, 5(2):241–259.

Young, J. G., Hernán, M. A., and Robins, J. M. (2014). Identification, estimation and approximation of risk under interventions that depend on the natural value of treatment using observational data. *Epidemiologic methods*, 3(1):1–19.