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 immunogenic response (due to vaccine) differed?

- Immunogenic response profiles only available for second-stage 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.
Two-phase sampling censors the complete data structure

- Complete (unobserved) data $X = (L, A, Y) \sim P_{0}^{X} \in M^{X}$, as per the full HVTN 505 trial cohort (Hammer et al. 2013):
  - $L$ (baseline covariates): sex, age, BMI, behavioral HIV risk,
  - $A$ (exposure): immune response profile for CD4+ and CD8+,
  - $Y$ (outcome of interest): HIV-1 infection status at week 28.
- Observed data $O = (C, CX) = (L, C, CA, Y); C \in \{0, 1\}$ is an indicator for inclusion in the second-stage sample.
NPSEM with static interventions

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

$$L = f_L(U_L); A = f_A(L, U_A); Y = f_Y(A, L, U_Y)$$

- Implies a model for the distribution of counterfactual random variables generated by interventions on the process.

- A static intervention replaces $f_A$ with a specific value $a$ in its conditional support $A \mid L$.

- This requires specifying a particular value of the exposure under which to evaluate the outcome \textit{a priori}. 
**NPSEM with stochastic interventions**

- *Stochastic interventions* modify the value $A$ would naturally assume by drawing from a modified exposure distribution.

- Consider the post-intervention value $A^* \sim G^*(\cdot \mid L)$; static interventions are a special case (degenerate distribution).

- Such an intervention generates a counterfactual random variable $Y_{G^*} := f_Y(A^*, L, U_Y)$, with distribution $P^\delta_0$.

- We aim to estimate $\psi_{0,\delta} := EP^\delta_0 \{ Y_{G^*} \}$, the counterfactual mean under the post-intervention exposure distribution $G^*$. 
Stochastic interventions for the causal effects of shifts

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

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

- Our estimand is \( \psi_{0,d} := \mathbb{E}_{P_d} \{ Y_{d(A,L)} \} \), mean of \( Y_{d(A,L)} \).

- Statistical target parameter is \( \Psi(P_{X|0}) = \mathbb{E}_{P_{X|0}} \overline{Q}(d(A, L), L) \), 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 \( d(A, L) \) defining \( G^*(\cdot | L) \).
Assumption 1: **Consistency**

\[ Y_{d(a_i, l_i)}^i = Y_i \text{ in the event } A_i = d(a_i, l_i), \text{ for } i = 1, \ldots, n \]

Assumption 2: **SUTVA**

\[ Y_{d(a_i, l_i)}^i \text{ does not depend on } d(a_j, l_j) \text{ for } i = 1, \ldots, n \text{ and } j \neq i, \text{ or lack of interference (Rubin 1978; 1980)} \]

Assumption 3: **Strong ignorability**

\[ A_i \perp Y_{d(a_i, l_i)}^i \mid L_i, \text{ for } i = 1, \ldots, n \]
Assumption 4: *Positivity (or overlap)*

\[ a_i \in \mathcal{A} \implies d(a_i, l_i) \in \mathcal{A} \text{ for all } l \in \mathcal{L}, \text{ where } \mathcal{A} \text{ denotes the support of } \mathcal{A} \text{ conditional on } L = l_i \text{ for all } i = 1, \ldots, n \]

- 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 \( a_i \in \mathcal{A} \) and \( l_i \in \mathcal{L} \).
Proposal: Evaluate outcome under an altered intervention distribution — e.g., \( P_\delta(g_0)(A = a \mid L) = g_0(a - \delta(L) \mid L) \).

Identification conditions for a statistical parameter of the counterfactual outcome \( \psi_{0,d} \) under such an intervention.

Show that the causal quantity of interest \( \mathbb{E}_0\{Y_{d(A,L)}\} \) is identified by a functional of the distribution of \( X \):

\[
\psi_{0,d} = \int_L \int_A \mathbb{E}_{P_0^X}\{Y \mid A = d(a, l), L = l\} \cdot q_{0,A}^X(a \mid L = l) \cdot q_{0,L}^X(l) d\mu(a) d\nu(l)
\]

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

- The efficient influence function (EIF) is:
  \[
  D(P^X_0)(x) = H(a, l)(y - \overline{Q}(a, l)) + \overline{Q}(d(a, l), l) - \Psi(P^X_0).
  \]

- The one-step estimator corrects bias by adding the empirical mean of the estimated EIF to the substitution estimator:
  \[
  \Psi_n^+ = \frac{1}{n} \sum_{i=1}^{n} \overline{Q}_n(d(A_i, L_i), L_i) + D_n(O_i).
  \]

- The TML estimator is built by updating initial estimates of \( \overline{Q}_n \) via a (logistic) tilting model, yielding
  \[
  \Psi_n^* = \frac{1}{n} \sum_{i=1}^{n} \overline{Q}_n^*(d(A_i, L_i), L_i).
  \]

- Both estimators are CAN even when nuisance parameters are estimated via flexible, machine learning techniques.
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:

\[
D(P_0^X)(o) = \frac{c}{\pi_0(y, l)} D^F(P_0^X)(x) - \left(1 - \frac{c}{\pi_0(y, l)}\right).
\]

\[
\mathbb{E}(D^F(P_0^X)(x) \mid C = 1, Y = y, L = l),
\]

- 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 \((g_0(L), \overline{Q}_0(A, L)) \times (\pi_0(Y, L), \mathbb{E}(D^F(P_0^X)(x) \mid C = 1, Y, L)))\).
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

https://twitter.com/nshejazi

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
“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.
• Correlate of Protection (CoP): immune marker statistically predictive of vaccine efficacy, not necessarily mechanistic.

• Mechanistic CoP (mCoP): immune marker that is mechanistically and causally 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.
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
Estimation in Two-Phase Designs

- Observed data structure: \( O = (L, A, Z, CM, Y, C) \)
  - \( A \in \{0, 1\} \): randomized vaccination assignment
  - \( Z \): post-vaccination confounder (e.g., unblinded risky behavior)
  - \( M \): candidate mCoPs (causal mediators)
  - \( Y \): symptomatic SARS-CoV-2 infection
  - \( C := f(Y, L) \): selection into second-phase sample

- But what about \( O = (L, A, Z, CM, \Delta, \tilde{T}, C) \)?
  - \( \tilde{T} = \min(T_F, T_C) \): possibly right-censored time to symptomatic SARS-CoV-2 infection
  - \( \Delta = \mathbb{I}(T_F < T_C) \): observed symptomatic SARS-CoV-2 infection
  - Can \( C \) still be a function of \( \tilde{T} \)?
Causal Mediation Analysis: Explanation and Mechanism

- **Identification assumptions:**
  - A1: No unmeasured confounding of \( \{A, Y\} \) relationship.
  - A2: No unmeasured confounding of \( \{M, Y\} \) relationship.
  - A3: No unmeasured confounding of \( \{A, M\} \) relationship.
  - A4: No \( \{M, Y\} \) 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 \( M \), no \( Z \), “cross-world” independence.
  - Stochastic (in)direct effects (Díaz and Hejazi 2020): continuous \( A \) and \( M \), no \( Z \); no “cross-world” exclusion.
  - Intervenational (in)direct effects (Díaz et al. 2020): binary \( A \), continuous \( M \), \( Z \) ok, no “cross-world” exclusion.
  - Stochastic interventional (in)direct effects (Hejazi et al. 2020): continuous \( A \) and \( M \), \( Z \) ok, no “cross-world” exclusion.
Appendix
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:

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

Such intervention policies account for the natural value of the intervention \( A \) 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).
- 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 $\mathbb{E} Y_{d(A, L)}$ or $\mathbb{E} Y_{d(L)}$.

- The authors also consider limits on implementing shifts $d(A, L)$, and address working in a longitudinal setting.
Literature: Díaz and van der Laan (2018)

- Builds on the original proposal, accommodating MTP-type shifts \( d(A, L) \) proposed after their earlier work.

- To protect against positivity violations, considers a specific shifting mechanism:

\[
d(a, l) = \begin{cases} 
  a + \delta, & a + \delta < u(l) \\
  a, & \text{otherwise}
\end{cases}
\]

- Proposes an improved “1-TMLE” algorithm, with a single auxiliary covariate for constructing the TML estimator.

- Our (first) contribution: implementation of this algorithm.
Nonparametric conditional density estimation

- To compute the auxiliary covariate $H(a, l)$, we need to estimate conditional densities $g(A \mid L)$ and $g(A - \delta \mid L)$.

- 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

$$g_{n,\alpha}(a \mid L) = \frac{\Pr(A \in [\alpha_{t-1}, \alpha_t) \mid L)}{\alpha_t - \alpha_{t-1}},$$

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

  - This is a classification problem, where we estimate the probability that a value of $A$ 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.
Díaz and van der Laan (2011) propose a re-formulation of this classification approach as a set of hazard regressions.

To effectively employ this proposed re-formulation, consider

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

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 \(A_i\) belongs, and the binary variables indicating \(A_i \in [\alpha_{t-1}, \alpha_t]\) are recorded.
Density estimation with the Super Learner algorithm

- To estimate $g(A \mid L)$ and $g(A - \delta \mid L)$, use a pooled hazard regression, spanning the support of $A$.

- 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.
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:**

\[
\sqrt{n}(\Psi(P_n^\star) - \Psi(P_0^X)) \rightarrow N(0, \text{Var}(D(P_0^X)(X)))
\]

- **Statistical inference:**

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 \(\sigma_n^2 = \frac{1}{n} \sum_{i=1}^{n} D^2(\cdot)(X_i)\).
Algorithm for TML estimation

1. Construct initial estimators $g_n$ of $g_0(A, L)$ and $Q_n$ of $Q_0(A, L)$, perhaps using data-adaptive regression techniques.

2. For each observation $i$, compute an estimate $H_n(a_i, l_i)$ of the auxiliary covariate $H(a_i, l_i)$.

3. Estimate the parameter $\epsilon$ in the logistic regression model

   \[
   \logit Q_{\epsilon, n}(a, l) = \logit Q_n(a, l) + \epsilon H_n(a, l),
   \]

   or an alternative regression model incorporating weights.

4. Compute TML estimator $\Psi_n$ of the target parameter, defining update $\overline{Q}_n^{*}$ of the initial estimate $\overline{Q}_n,\epsilon_n$:

   \[
   \Psi_n = \Psi(P_n^{*}) = \frac{1}{n} \sum_{i=1}^{n} \overline{Q}_n^{*}(d(A_i, L_i), L_i). 
   \]
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 \(g_n(A, L)\) and \(Q_n(A, L)\), weighting by the sampling mechanism estimate \(\pi_n(Y, L)\).

3. With the approach described for the full data case, compute \(H_n(a_i, l_i)\), 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 \(\frac{1}{n} \sum_{i=1}^{n} EIF_i < \frac{1}{n}\).
Figure 2: Relative performance of reweighted and augmented estimators.
A linear modeling perspective

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

\[
\mathbb{E} Y_{A+\delta} - \mathbb{E} Y_A = [\beta_0 + \beta_1 (\mathbb{E} A + \delta)] - [\beta_0 + \beta_1 (\mathbb{E} A)] \\
= \beta_0 - \beta_0 + \beta_1 \mathbb{E} A - \beta_1 \mathbb{E} A + \beta_1 \delta \\
= \beta_1 \delta
\]

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

- Consider a data structure: \((Y_a, a \in A)\).

- To posit a linear model, let \(Y_a = \beta_0 + \beta_1 a + \epsilon_a\) for \(a \in A\), with error \(\epsilon_a \sim N(0, \sigma_a^2) \ \forall a \in A\).

- For the counterfactual outcomes \((Y_{a'} + \delta, Y_{a'})\), their difference, \(Y_{a' + \delta} - Y_{a'}\), for some \(a' \in A\), may be expressed

\[
\mathbb{E}Y_{a' + \delta} - \mathbb{E}Y_{a'} = [\beta_0 + \beta_1 (a' + \delta) + \mathbb{E}\epsilon_{a' + \delta}] - [\beta_0 + \beta_1 a' + \mathbb{E}\epsilon_{a'}] = \beta_1 \delta
\]

- Thus, a unit shift for \(a' \in A\) (i.e., \(\delta = 1\)) may be seen as inducing a change in the difference in the counterfactual outcomes of magnitude \(\beta_1\).
Slope in a semiparametric model

- Consider the stochastic intervention $g^*(\cdot \mid L)$:

$$
\mathbb{E} Y_{g^*} = \int \int_a \mathbb{E}(Y \mid A = a, L)g(a - \delta \mid L) \cdot da \cdot dP_0(L)
$$

$$
= \int \int_z \mathbb{E}(Y \mid A = z + \delta, L)g(z \mid L) \cdot dz \cdot dP_0(L),
$$

defining the change of variable $z = a - \delta$.

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

$$
\mathbb{E} Y_{g^*} - \mathbb{E} Y = \int \int_z \left[ \mathbb{E}(Y \mid A = z + \delta, L) - \mathbb{E}(Y \mid A = z, L) \right] g(z \mid L) \cdot dz \cdot dP_0(L)
$$

$$
= [\beta(z + \delta) + \theta(L)] - [\beta z + \theta(L)]
$$

$$
= \beta \delta
$$
References


