# Vaccine efficacy assessment under two-phase sampling based on the causal effects of stochastic interventions

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joint work with David Benkeser and Mark van der Laan

# 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**: How can HIV-1 vaccines be improved by modulating immunogenic CD4+ or CD8+ response profiles?

# HVTN 505 trial examined new antibody boost vaccines

- HIV Vaccine Trials Network (HVTN) 505 vaccine efficacy RCT with $n = 2504$ (Hammer et al. 2013).
- Immunogenic response profile only available for second-stage sample of $n = 189$ (Janes et al. 2017).
- Two-phased sampling mechanism: 100% inclusion rate if HIV-1 positive in week 28; variable otherwise.
- **Question:** How would HIV-1 infection risk in week 28 have differed had immunogenic response (due to vaccine) differed?

# Two-phase sampling censors the complete data structure

- Complete, unobserved data $X = (W, A, Y) \sim P_0^X \in \mathcal{M}_{NP}^X$, as per the full HVTN 505 RCT (Hammer et al. 2013):
  - $W$ — baseline covariates: sex, age, BMI, behavioral HIV risk,
  - $A$ — intervention: immune response profile for CD4 and CD8,
  - $Y$ — outcome of interest: HIV-1 infection status by week 28.
- Observed data $O = (\Delta, \Delta X) = (W, \Delta, \Delta A, Y)$, $\Delta \in \{0, 1\}$, as per the second-stage sample of Janes et al. (2017).

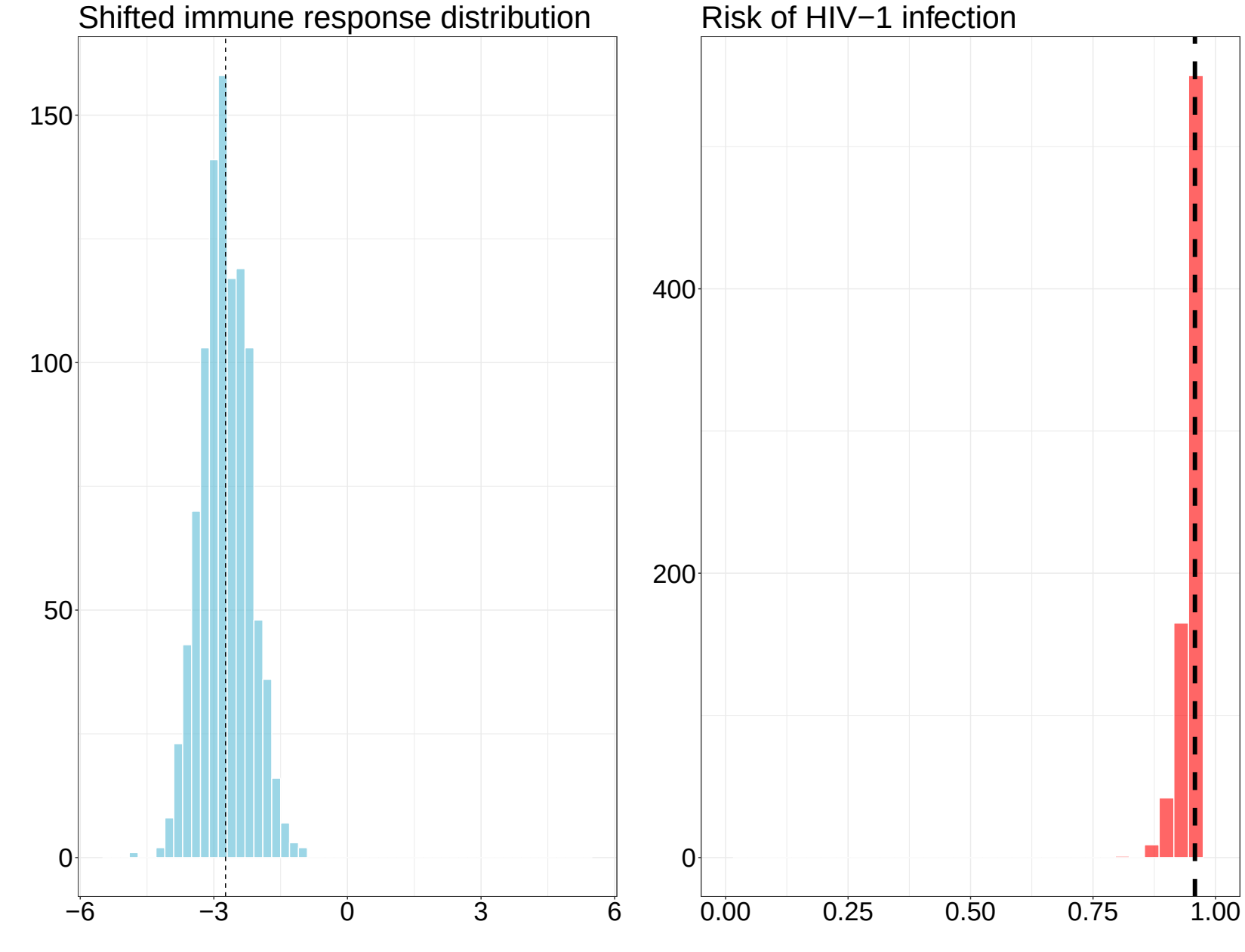
# Stochastic interventions define the causal effects of shifts

- Causal estimand: counterfactual mean of HIV-1 infection under a *shifted* immunogenic response distribution.
- Díaz and van der Laan (2012; 2018): *Shift* interventions?

$$d(a, w) = \begin{cases} a + \delta, & \text{if plausible} \\ a, & \text{otherwise} \end{cases}$$

- Díaz and van der Laan (2012; 2018) give a statistical target parameter and influence function for the complete data case.
- **Challenge:** parameter estimation requires conditional density estimation. Nonparametric options?

# HIV-1 risk under stochastically shifted immune responses



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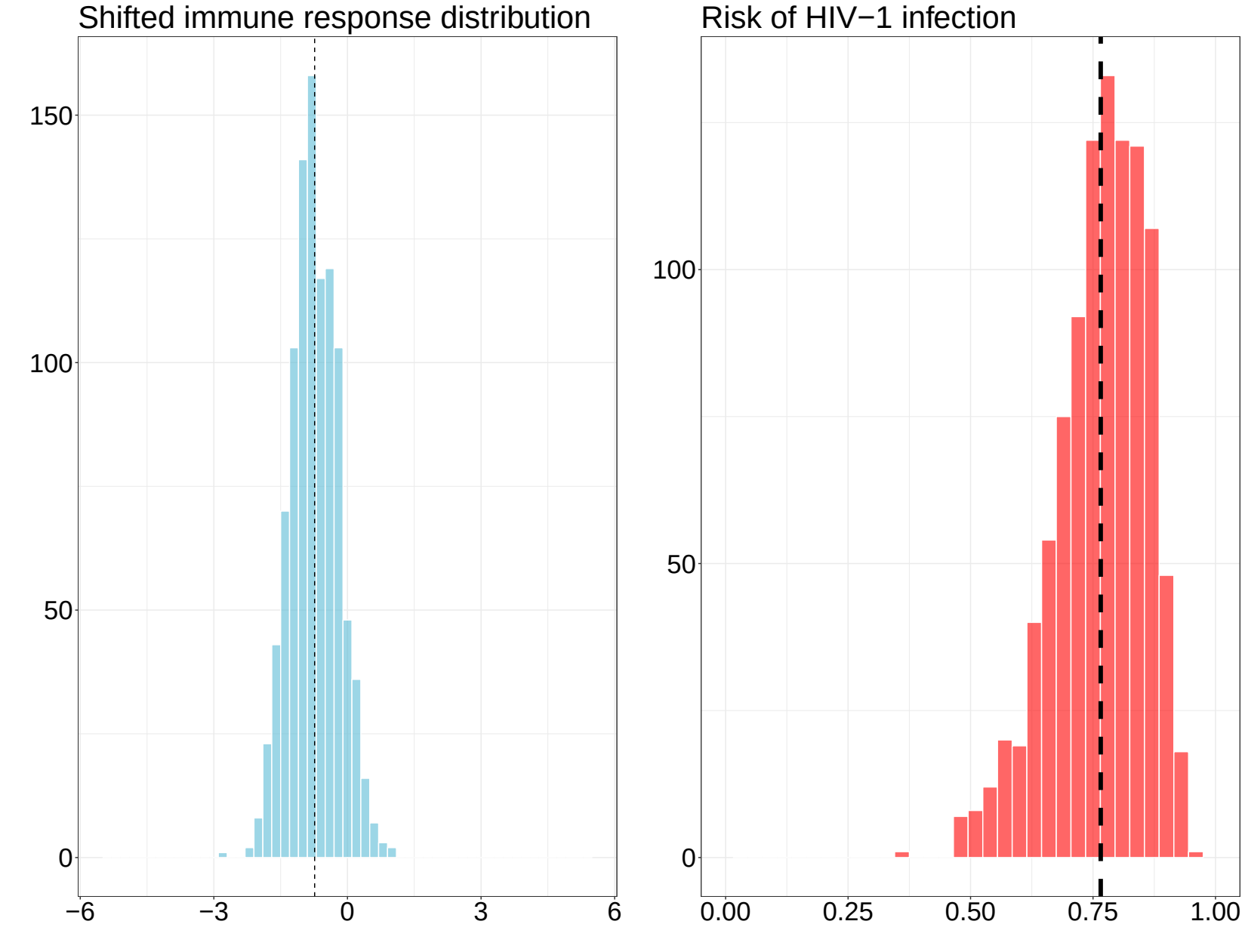

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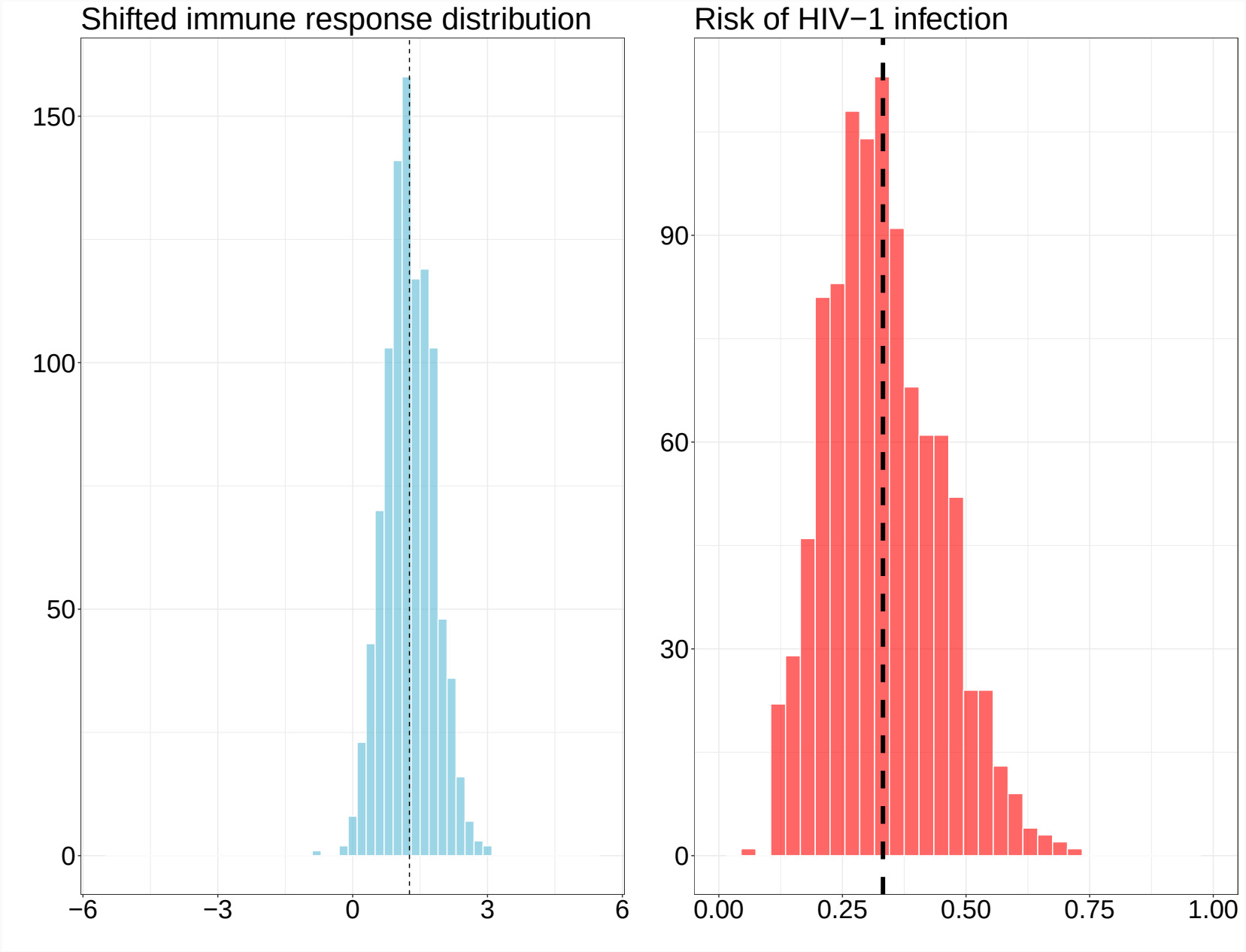

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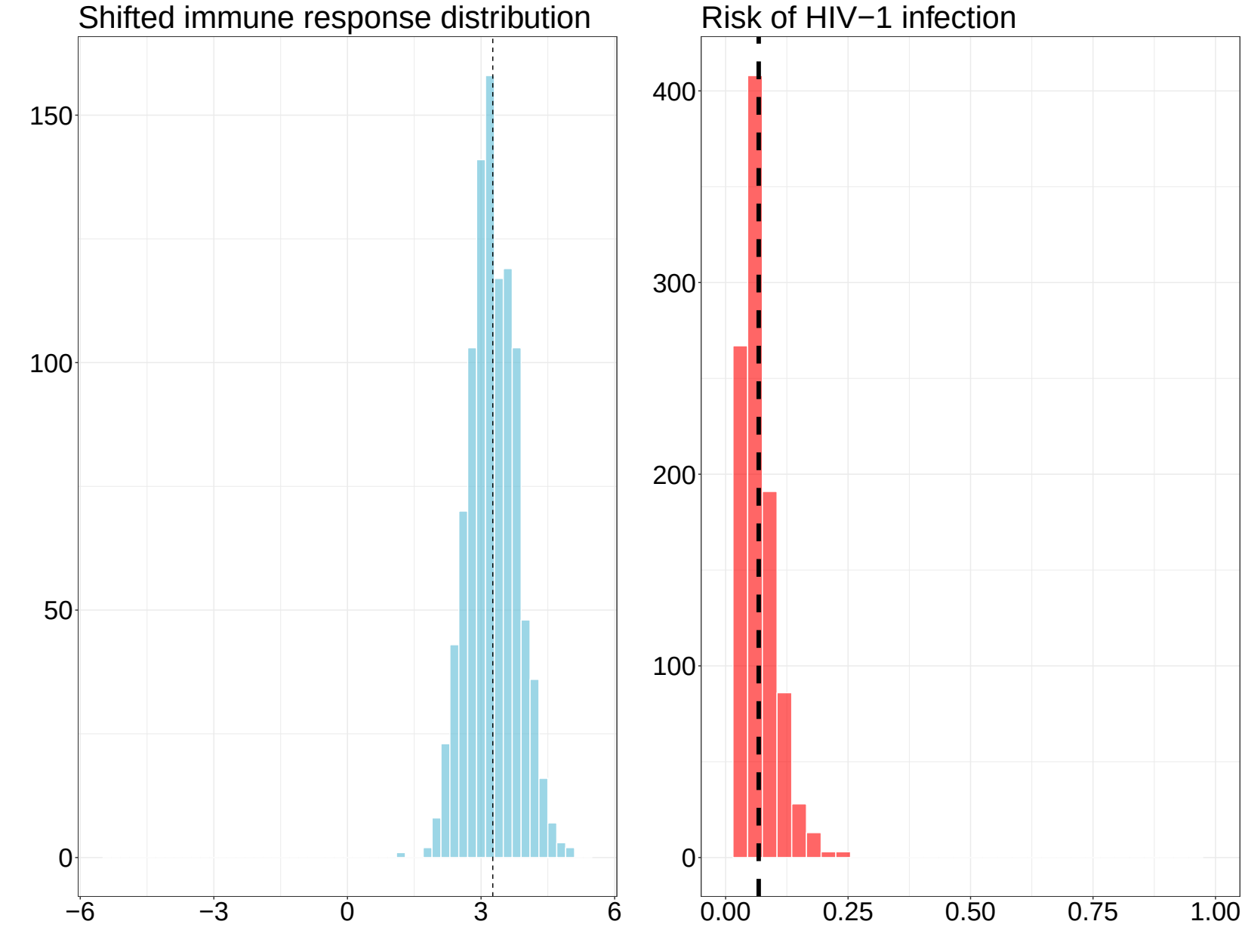

# Efficient estimators in spite of two-phase sampling

- What if sampling mechanism $\pi_0(Y, W) = \mathbb{P}(\Delta = 1 \mid Y, W)$ is not known by design? Nonparametric estimation of $\pi_0(Y, W)$?
- Building on Rose and van der Laan (2011), we provide
  - asymptotically linear and nonparametric-*efficient* estimators;
  - multiply *robust*, with 2 forms of double robustness;
  - Gaussian limiting distributions and Wald-type CIs.
- New open source software for deploying such estimators:
  - `https://github.com/nhejazi/haldensify` (densities)
  - `https://github.com/nhejazi/txshift` (AIPW, TMLE)
  - `https://github.com/tlverse/tmle3shift` (TMLE)

# How does this help in fighting the HIV-1 epidemic?

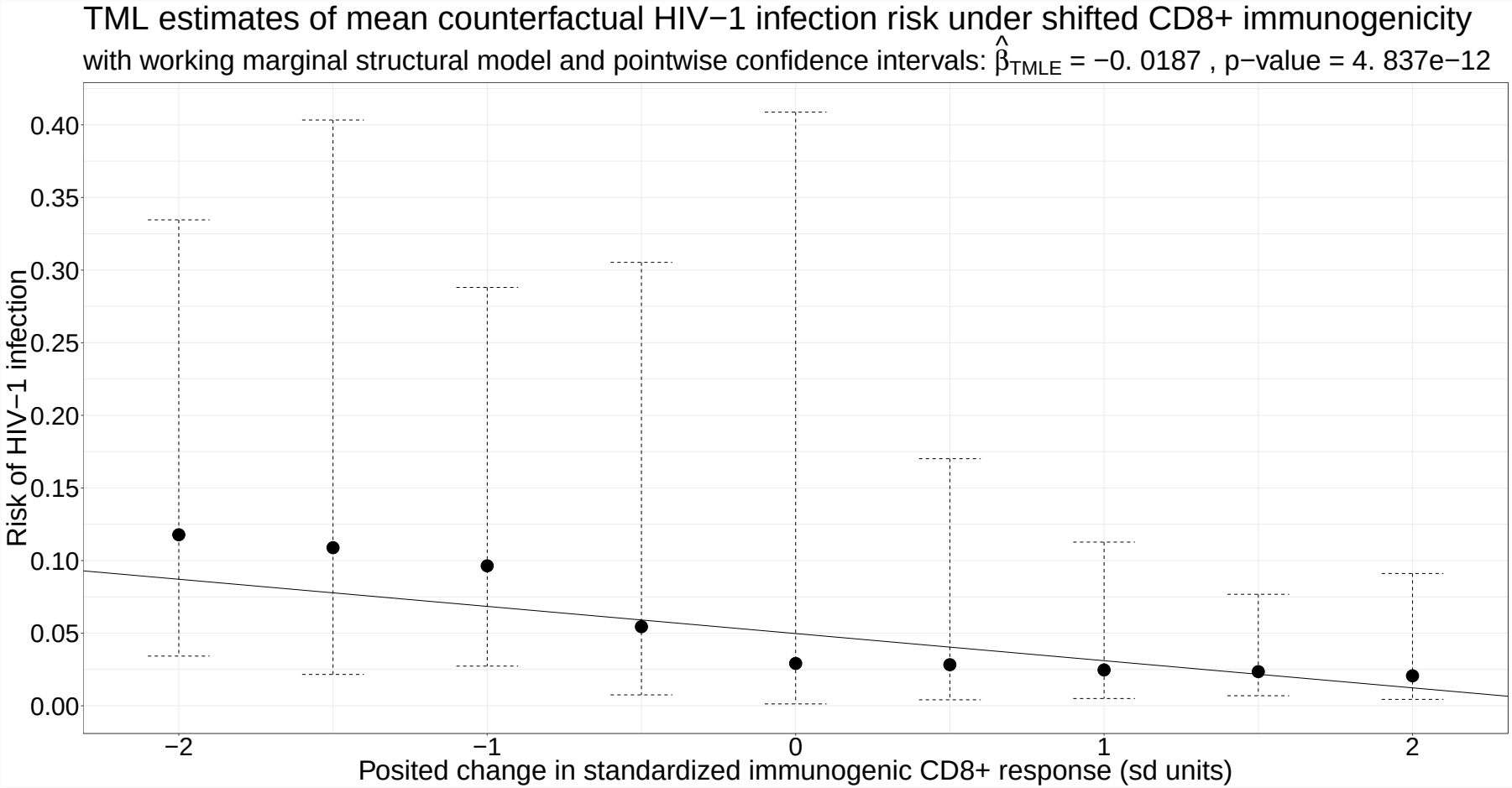


**Figure 1:** Analysis of HIV-1 risk as a function of CD8+ immunogenicity, using R package `txshift` (`https://github.com/nhejazi/txshift`.)

# References


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# Thank you.

Slides: bit.ly/2019_bstars_shift 


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