Symmetric Vaccine Efficacy

Interpretable Estimation and Inference for Vaccine Trials

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outline

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Motivation
What started this journey?

2

Derivation
Math behind SVE & uncertainty

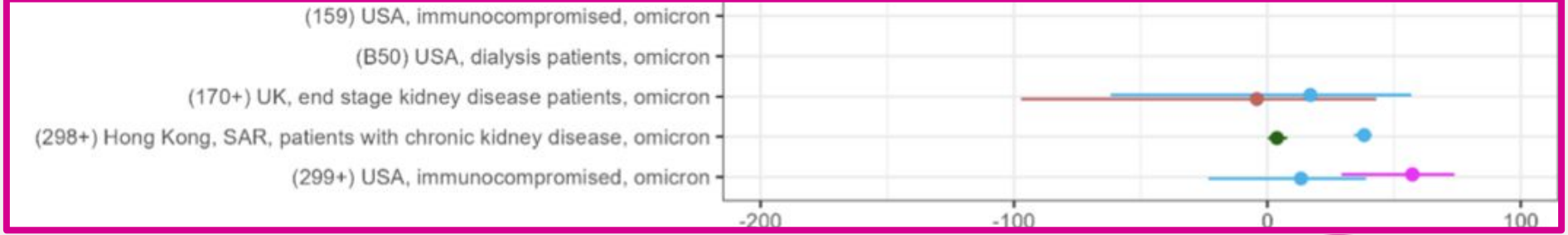
3

Application
How does it compare?

(D'Agostino McGowan, Lotspeich, Hudgens (2026) Biometrics)
arXiv:2512.07739

Motivation

Vaccine Effectiveness Among Immunocompromised Persons, Omicron Variant



Results of COVID-19 Vaccine Effectiveness Studies: An Ongoing Systematic Review

Motivation

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(D'Agostino McGowan, Lotspeich, Hudgens (2026) Biometrics)
arXiv:2512.07739

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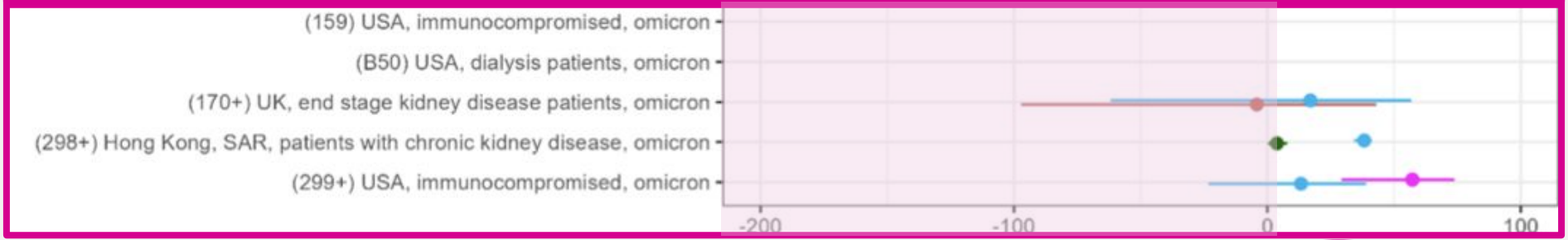

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Sarah Lotspeich

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Symmetric Vaccine Efficacy

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(D'Agostino McGowan, Lotspeich, Hudgens (2026) Biometrics)
arXiv:2512.07739

1 Practical application

MY FAVORITE THINGS

1 **Practical application**

2 **Cute Math**

(D'Agostino McGowan, Lotspeich, Hudgens (2026) Biometrics)
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VACCINE EFFICACY

$$\text{VE} = 1 - \frac{p_1}{p_0}$$

Probability of infection in the vaccinated group

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VACCINE EFFICACY

Probability of infection in the vaccinated group

$$\mathrm{VE} = 1 - \frac{p_1}{p_0}$$

Probability of infection in the unvaccinated group

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VACCINE EFFICACY

Bounded above by 1

unbounded below

$$\mathrm{VE} = 1 - \frac{p_1}{p_0}$$

(D'Agostino McGowan, Lotspeich, Hudgens (2026) Biometrics)
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VACCINE EFFICACY

- Because VE is unbounded below, estimates and confidence intervals can take on extreme negative values.
- This occurs when the vaccine group has higher infection rates or when the number of infections is small.
- Extreme negative values make interpretation difficult, vaccines often work at the population level, so we need population-level understanding

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SYMMETRIC VACCINE EFFICACY

if $p_0 > p_1$

$$1 - \frac{p_1}{p_0}$$

if $p_1 > p_0$

$$\frac{p_0}{p_1} - 1$$

(D'Agostino McGowan, Lotspeich, Hudgens (2026) Biometrics)
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Derivation

SYMMETRIZATION

- Berry & Ayers (2006) symmetrized percent change for treatment comparisons from baseline; improved interpretability without loss of statistical efficiency
- van der Laan et al. (2007) switch causal relative risk for binary outcomes in randomized trials with non-compliance
- Baker & Jackson (2018) generalized relative risk reduction in the context of meta-analyses

OUR GOAL

- Provide a bounded, interpretable measure of vaccine effect ranging from -1 (maximal harm) to 1 (maximal protection)
- Develop inferential methods including profile likelihood and delta method confidence intervals that have not previously been studied for this class of parameters.

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SYMMETRIC VACCINE EFFICACY

$$\text{SVE} = \frac{p_0 - p_1}{\max\left(p_0, p_1\right)}$$

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When the vaccine is protective, SVE behaves **identically to traditional vaccine efficacy** .

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SYMMETRIC VACCINE EFFICACY

$$\text{SVE} = \frac{p_0}{p_1} - 1$$

Negative SVE captures the **proportional decrease in risk from not being vaccinated**

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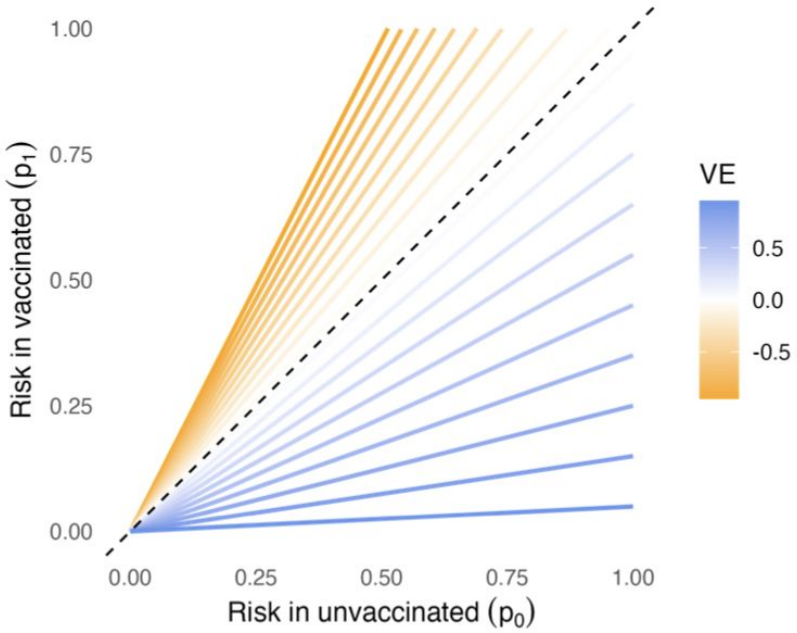
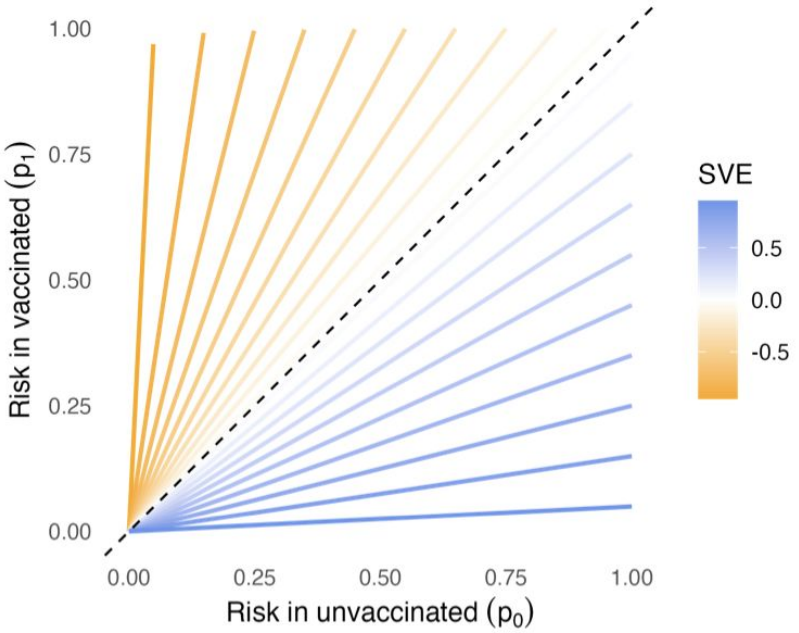


(a) Traditional Vaccine Efficacy (VE)



(b) Symmetric Vaccine Efficacy (SVE)

L'Abbe plots illustrating iso-effect lines

(D'Agostino McGowan, Lotspeich, Hudgens (2026) Biometrics)
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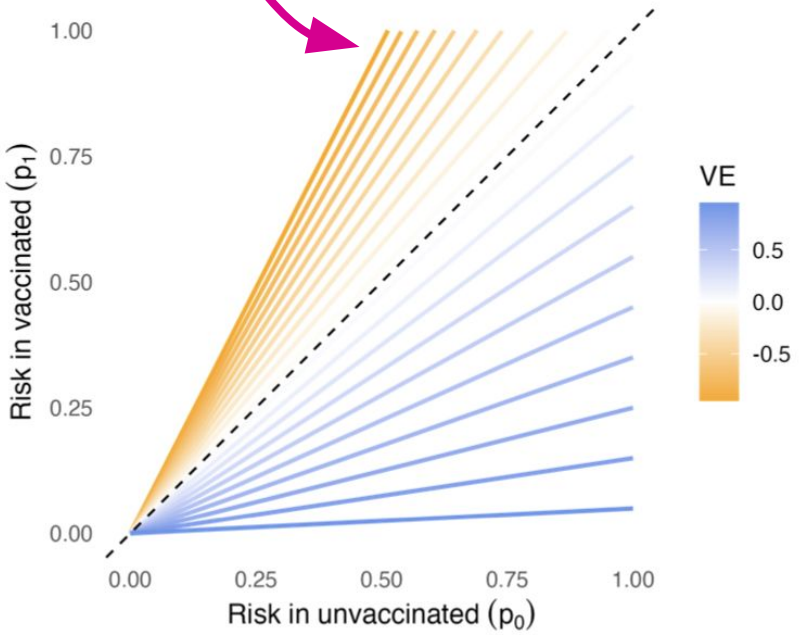
Each line represents a fixed effect size, with 20 evenly spaced values from -0.95 to 0.95



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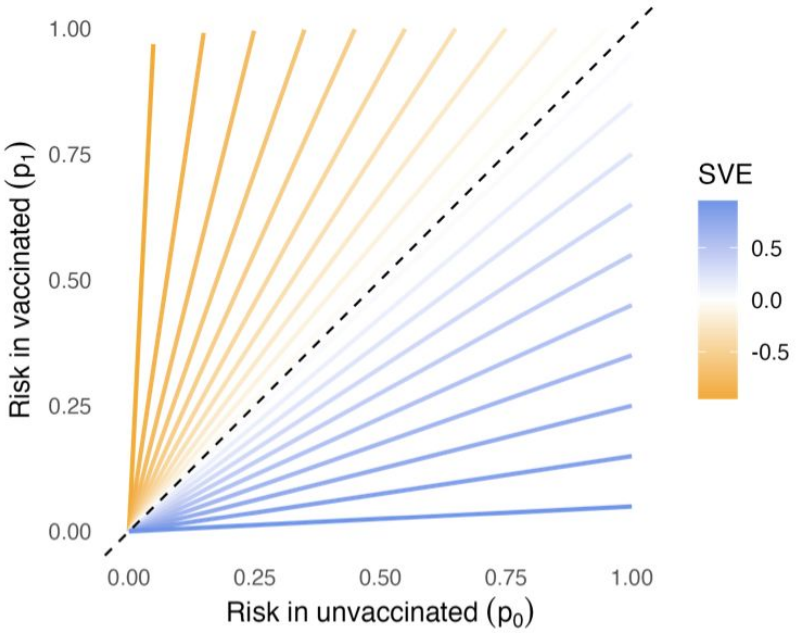

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$$X_0 \sim \text{Binomial}(n_0, p_0)$$

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Number of infections observed in the unvaccinated and vaccinated groups

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ESTIMATOR

$$\widehat{\mathrm{SVE}} = \frac{\hat{p}_0 - \hat{p}_1}{\max(\hat{p}_0, \hat{p}_1)}$$

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PROFILE LIKELIHOOD

$$\ell_p(\text{SVE}) = \begin{cases} \sup\limits_{p_0 \in (0,1)} \ell(p_0, p_0(1-\text{SVE})) & \text{if SVE} \in [0,1), \\ \sup\limits_{p_1 \in (0,1)} \ell(p_1(1+\text{SVE}), p_1) & \text{if SVE} \in (-1,0). \end{cases}$$

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There are two cases, each with a one-dimensional maximization over either p_0 or p_1 which can be solved using standard one-dimensional numerical optimization algorithms.

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PROFILE LIKELIHOOD

$$H_0 : \text{SVE} = s$$

$$\Lambda(s) = 2\{\ell(\hat{p}_0, \hat{p}_1) - \ell_p(s)\}$$

We can test a null hypothesis, SVE = s where the likelihood ratio statistic is defined as twice the gap between the unconstrained log likelihood and the profile log likelihood at s

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PROFILE LIKELIHOOD

$$\{s \in (-1, 1) : \Lambda(s) \leq \chi^2_{1,1-\alpha}\}$$

Inverting this test gives a confidence interval (the set of values s that would not be rejected at level α)

(D'Agostino McGowan, Lotspeich, Hudgens (2026) Biometrics)
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WALD INTERVAL

$$\widehat{\mathrm{SVE}} \pm z_{1-\alpha/2}\sqrt{\widehat{\mathrm{Var}}(\widehat{\mathrm{SVE}})}$$

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WALD INTERVAL

$$\widehat{\mathrm{Var}}(\widehat{\mathrm{SVE}}) = \frac{\hat{p}_1^2\hat{\sigma}_0^2 + \hat{p}_0^2\hat{\sigma}_1^2}{\{\max(\hat{p}_0, \hat{p}_1)\}^4}$$

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WALD INTERVAL

$$\widehat{\mathrm{SVE}} \pm z_{1-\alpha/2}\sqrt{\widehat{\mathrm{Var}}(\widehat{\mathrm{SVE}})}$$

One issue is this interval can exceed the bounds (i.e., go beyond -1 and 1)

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TANH-WALD INTERVAL

$$\left[\tanh\left(\widehat{u} - z_{1-\alpha/2}\sqrt{\widehat{\mathrm{Var}}(\widehat{u})}\right), \tanh\left(\widehat{u} + z_{1-\alpha/2}\sqrt{\widehat{\mathrm{Var}}(\widehat{u})}\right)\right]$$

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We can use the inverse hyperbolic tangent to transform the SVE & then back-transform to force the interval to be between -1 and 1 (originally used for correlation!)

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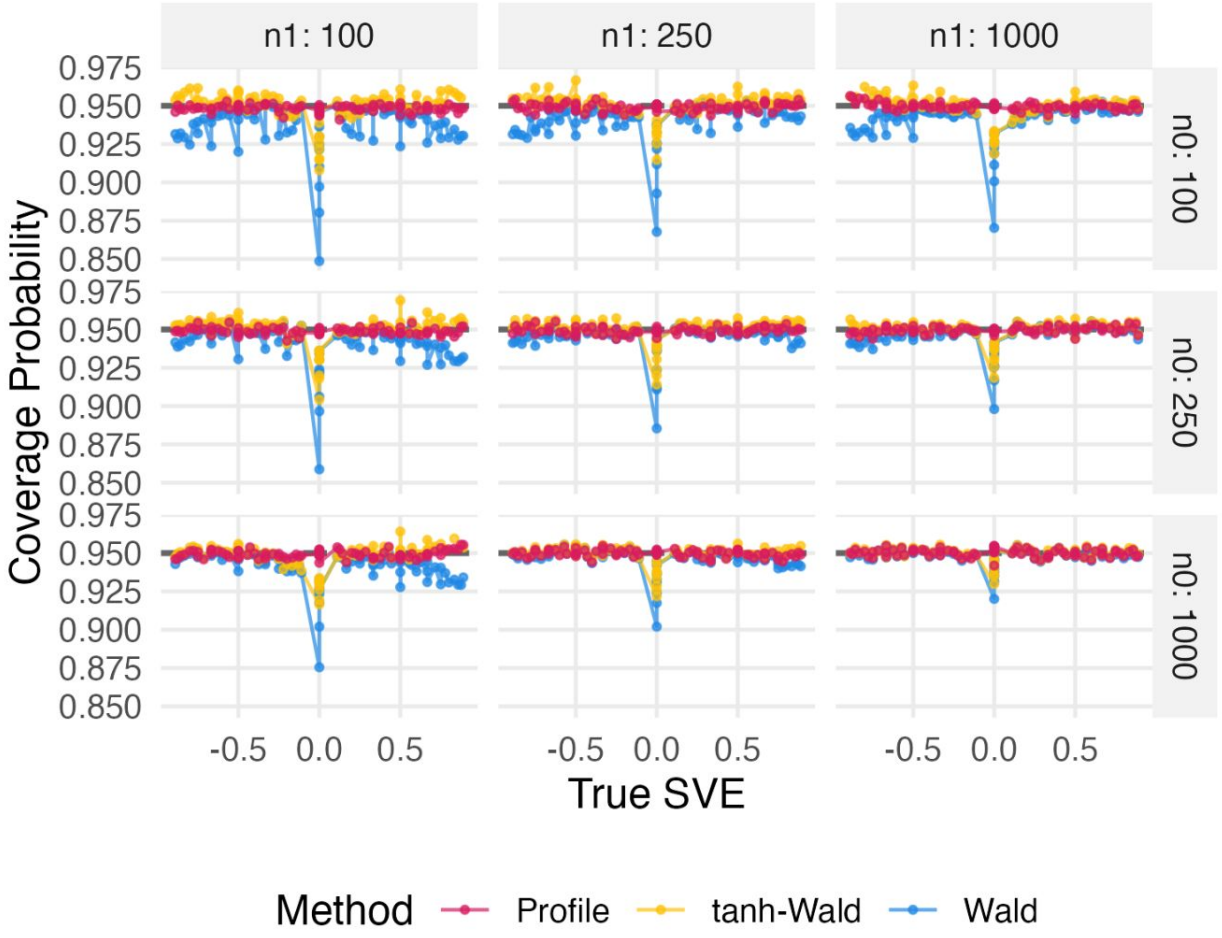
Operating Characteristics



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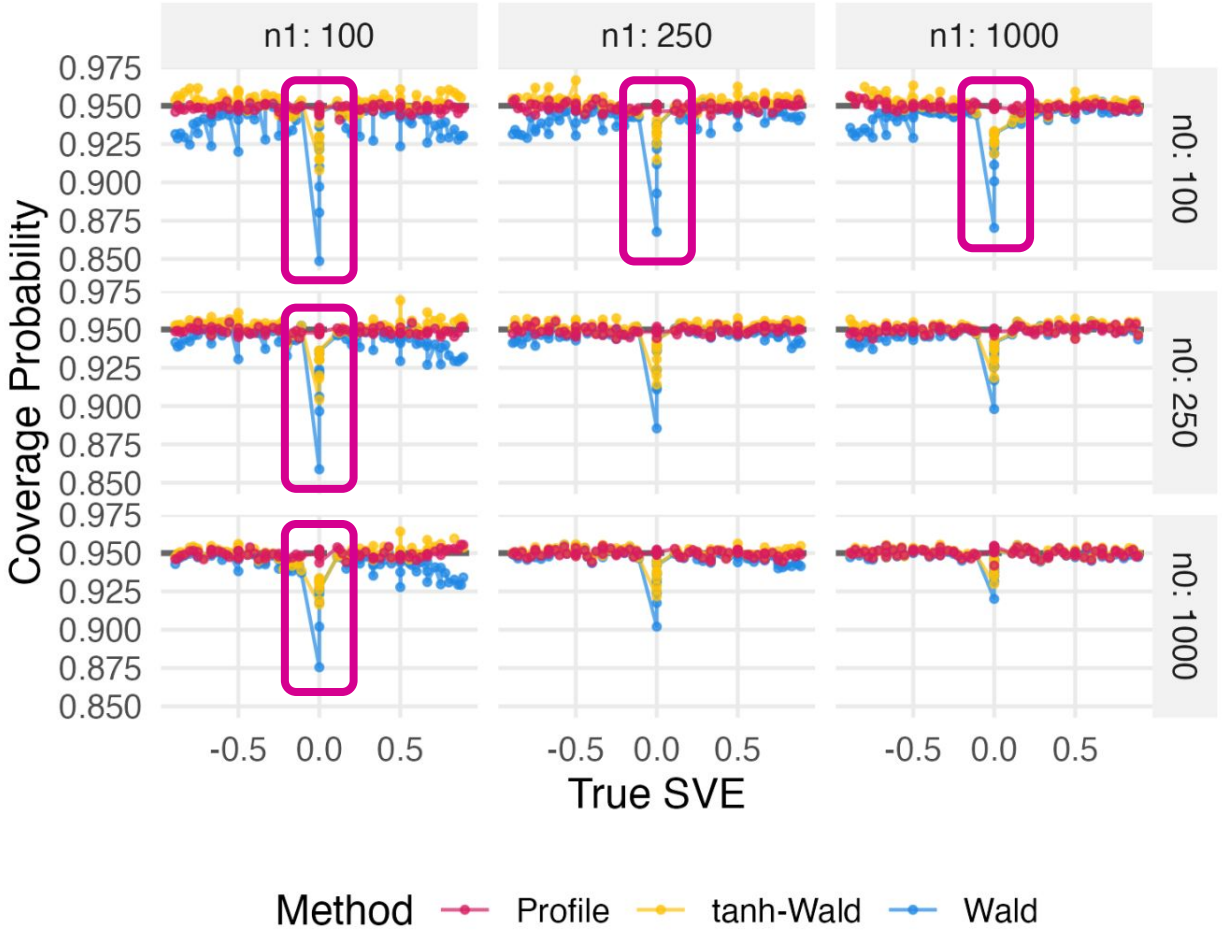

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BIAS CORRECTION

$$\widehat{\mathrm{SVE}}_{\mathrm{BC}} = \begin{cases} \widehat{\mathrm{SVE}} + \dfrac{\hat{p}_1(1-\hat{p}_0)}{n_0\hat{p}_0^2} & \text{if } \hat{p}_0 > \hat{p}_1, \\ \widehat{\mathrm{SVE}} - \dfrac{\hat{p}_0(1-\hat{p}_1)}{n_1\hat{p}_1^2} & \text{if } \hat{p}_1 > \hat{p}_0, \\ \widehat{\mathrm{SVE}} & \text{if } \hat{p}_0 = \hat{p}_1 \end{cases}$$

SVE is consistent but slightly biased in small samples (which we can approximate with a second-order Taylor expansion)

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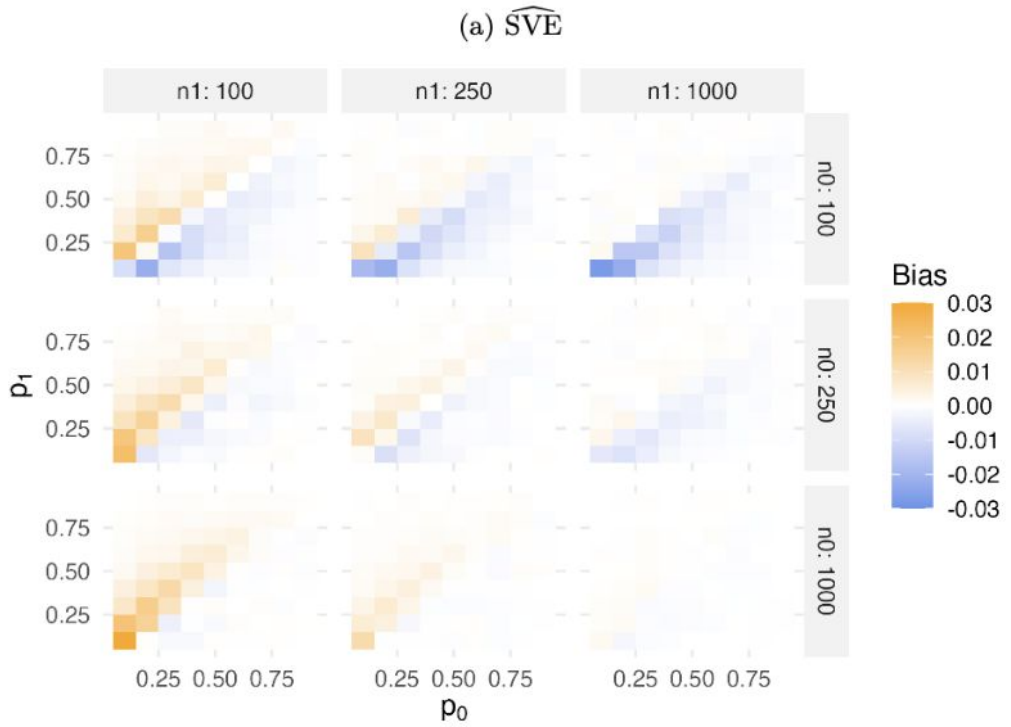
SVE Bias



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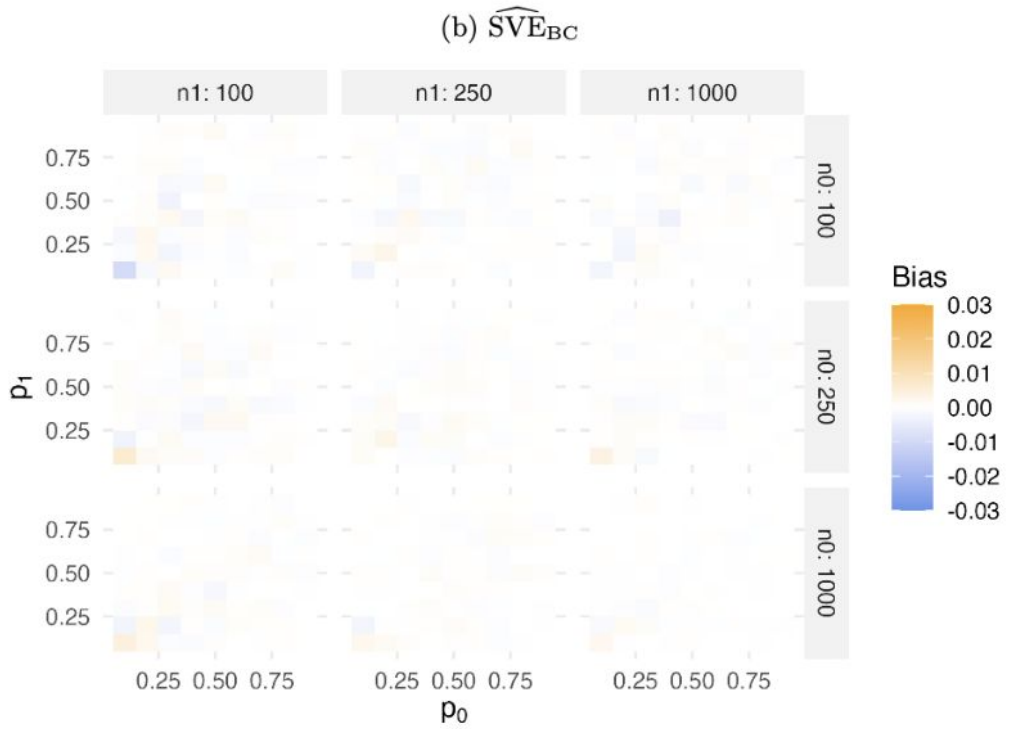
SVE Bias Corrected



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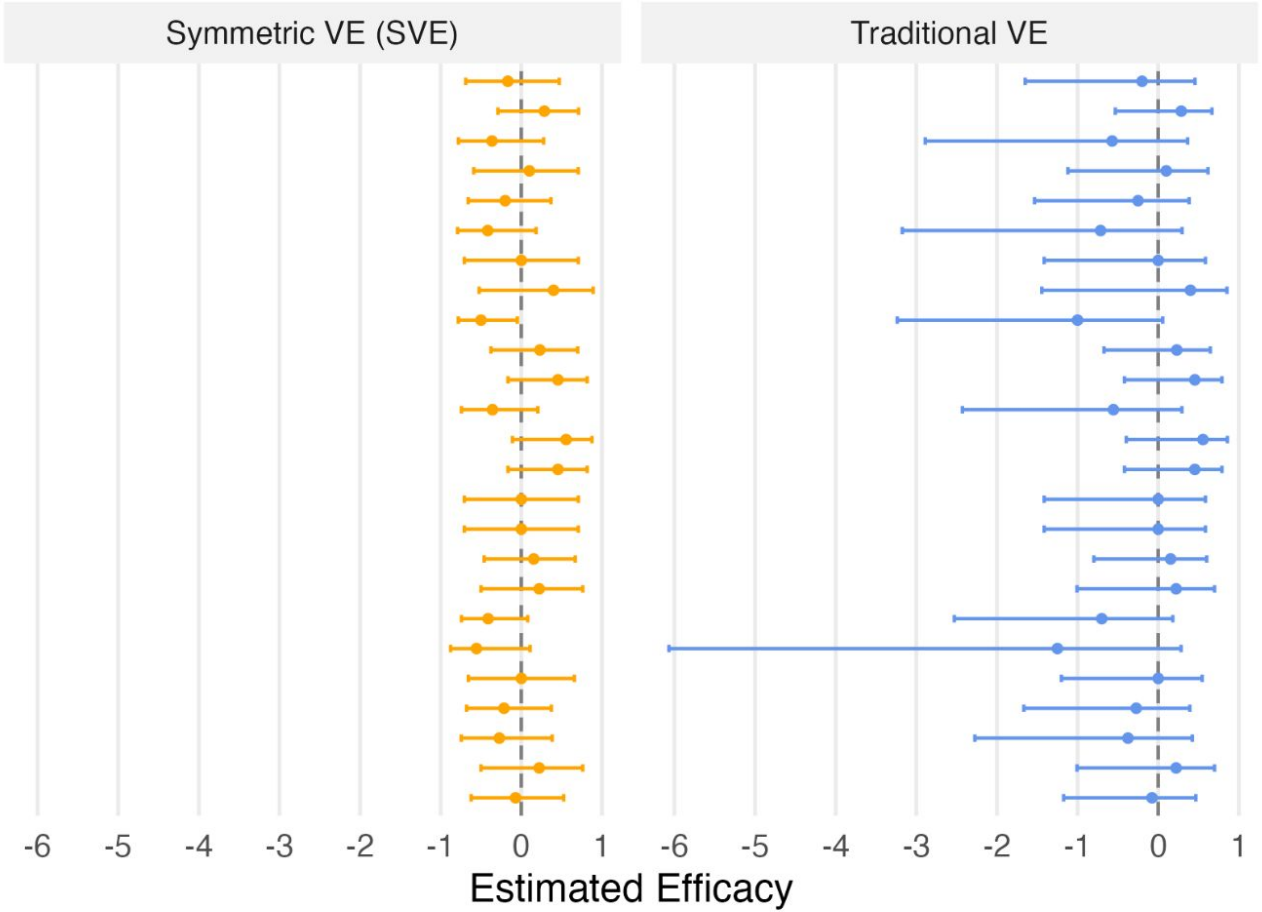
Application

Under the null



$p_0=p_1=0.1$

$n_0=n_1=100$

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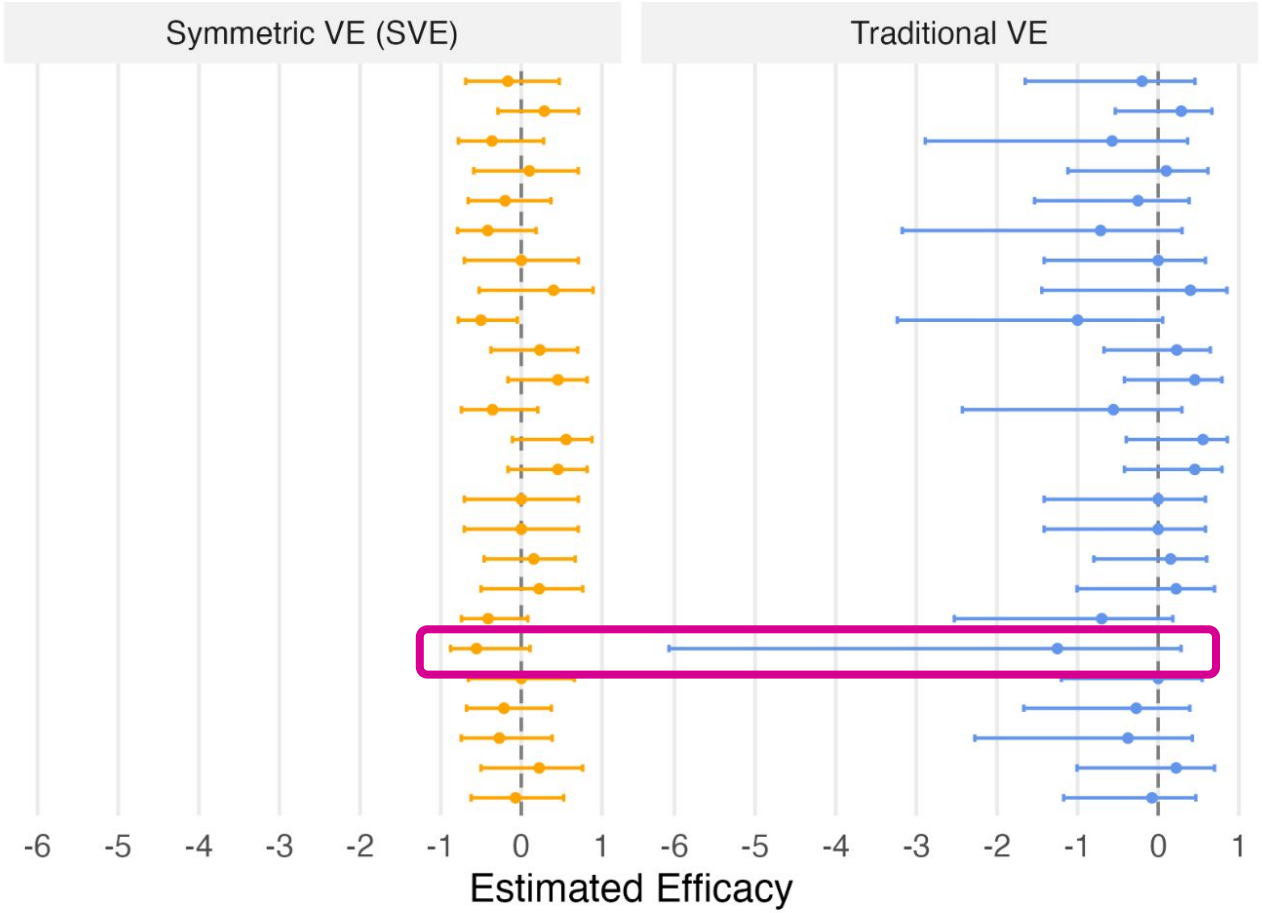
Under the null



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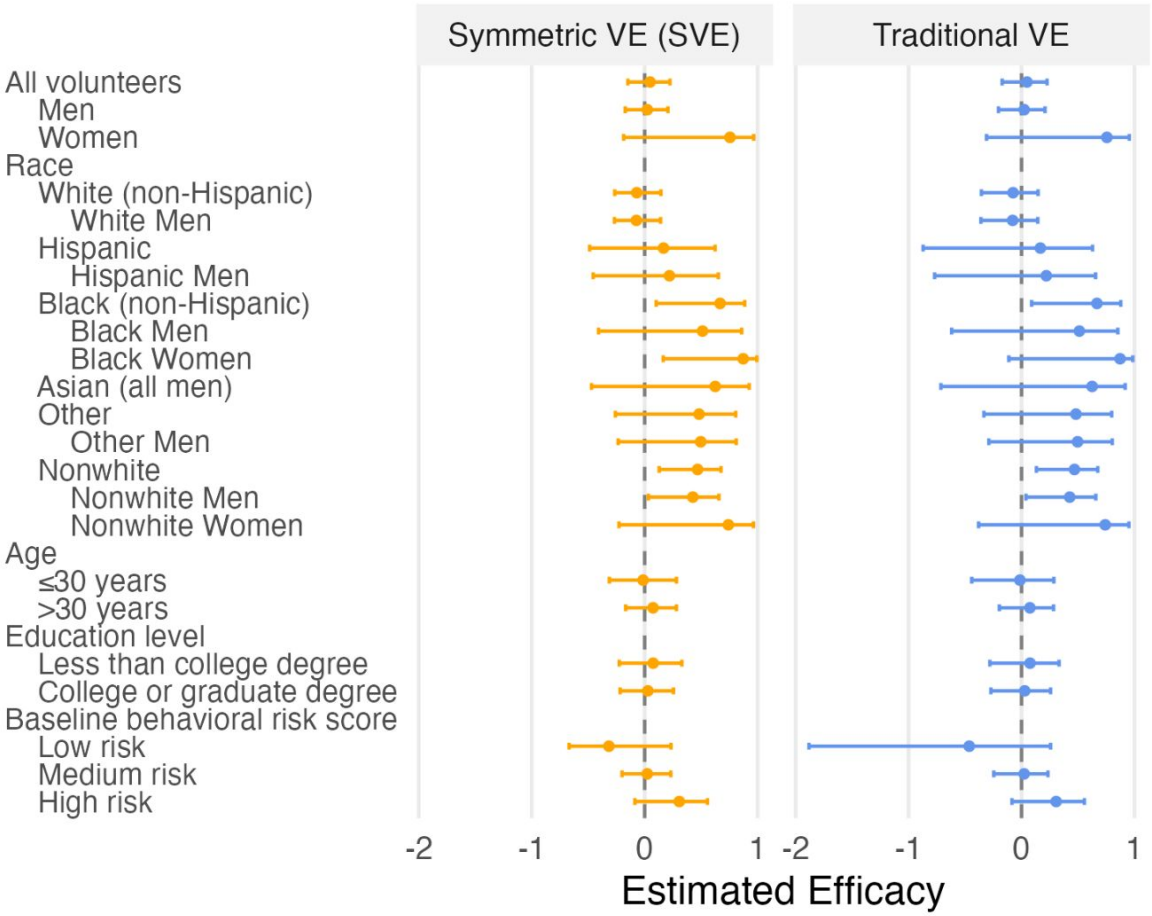
Real Data



rgp120 HIV-1 vaccine trial

5,403 participants, randomized 2:1
n_1 = 3,598 vaccine
n_0 = 1,805 placebo
Endpoint: HIV-1 seroconversion

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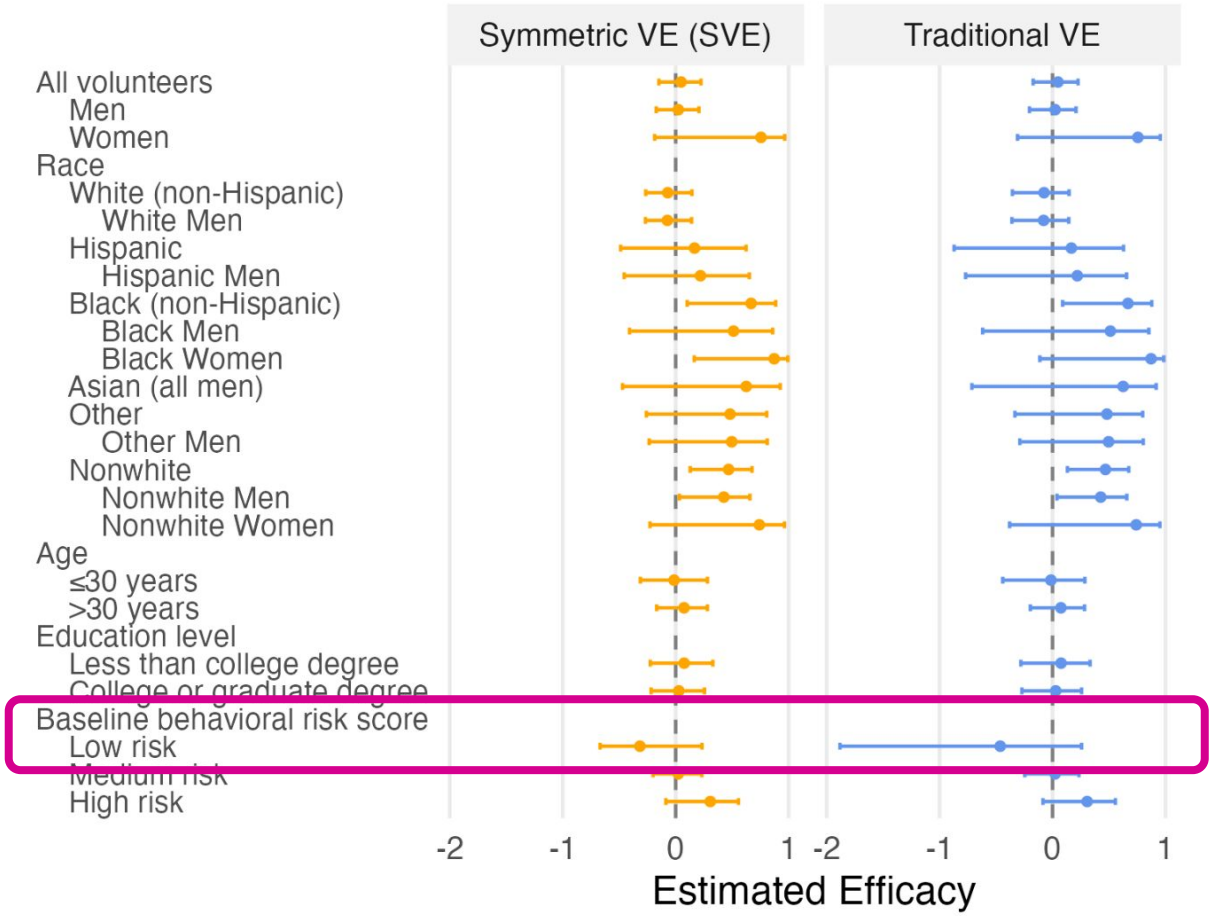

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n_0 = 1,805 placebo
Endpoint: HIV-1 seroconversion

(D'Agostino McGowan, Lotspeich, Hudgens (2026) Biometrics)
arXiv:2512.07739

R package

```
devtools::install_github("LucyMcGowan/sve")
library(sve)
est_sve(x0 = 100, x1 = 50, n0 = 1000, n1 = 1000)
#> estimate lower upper level method
#> 0.50     0.31  0.64  0.95  Profile
```

R package

```
library(survival)
fit <- coxph(Surv(time, status) ~ vaccination + age +
             baseline_risk, data = sim_trial_data)
sve_from_model(model = fit, data = sim_trial_data,
               effect_name = "vaccination")
#> estimate lower upper level method
#> 0.68     0.59  0.75  0.95  Profile
```

(D'Agostino McGowan, Lotspeich, Hudgens (2026) Biometrics)
arXiv:2512.07739

THANKS!

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