HIV VACCINE TRIALS NETWORK

Methods for Comparing Mark-specific Hazards and Cumulative Incidence Functions Between Two Groups, with Application to HIV Vaccine Trials

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Outline

- Motivating Example: HIV vaccine efficacy trial
- Statistical Methods
  - Hypothesis testing
  - Estimation
- Illustration

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Example: HIV Vaccine Efficacy Trial

- **Primary objective:** Assess vaccine efficacy (VE) to prevent HIV infection
- **Secondary objective:** Assess if and how VE varies with genotypic/phenotypic characteristics of HIV
- For each infected subject, measure the **distance** V between the infecting virus and the virus(es) represented in the vaccine
- **Available data:**
  - Vaccine group: $(T_{1i}, \delta_{1i}, \delta_{1i}V_{1i}), \quad i = 1, \cdots, n_1$
  - Placebo group: $(T_{2i}, \delta_{2i}, \delta_{2i}V_{2i}), \quad i = 1, \cdots, n_2$

Example: HIV Vaccine Efficacy Trial

- **Case 1:** V a small number of ordered categories
  - E.g.: $V \in \{0, 1, 2, 3+\}$ substitutions/deletions in the HIV V3 loop tip sequence GPGRAF
  - For each strain category j, can study $VE(t, j)$ using cause-specific hazard functions or cumulative incidence functions:

$$VE(t,j) = 1 - \frac{\lambda_{1j}(t)}{\lambda_{2j}(t)} \quad \text{or} \quad VE(t,j) = 1 - \frac{F_{1j}(t)}{F_{2j}(t)}$$

Prentice et al. (1978, Biometrics);
Gilbert (2000, Statistics in Medicine)

Example: HIV Vaccine Efficacy Trial

- **Case 2:** V a large number of ordered categories
  - E.g.: percent amino acid mismatch computed over hundreds or thousands of positions

    $\Rightarrow$ Treat V as continuous, $V \in [0, 1]$
  - Gilbert et al. (1999, Biometrika; 2000, Annals of Statistics) developed semiparametric methods for studying $OR(v)$
    - $OR(v) =$ odds that the infecting strain has distance v for vaccine versus placebo recipients

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Example: HIV Vaccine Efficacy Trial

- **Semiparametric biased sampling model:**

$$F_1(v,\theta) = \frac{\int_0^v w(z,\theta)dF_2(z)}{\int_0^\infty w(z,\theta)dF_2(z)}$$

- **Limitations:**
  - Interpretation conditional on infection
  - $OR(v)$ assumed to satisfy a parametric form
  - Does not account for time to HIV infection

Statistical Methods

- **Objective:** Develop methods for testing and estimation of $VE(t,v)$ defined based on continuous mark-specific hazard and cumulative incidence functions
  - Mark-specific hazard functions:

$$\lambda_k(t,v) = \lim_{h_1,h_2 \to 0} P\{T_k \in [t, t+h_1), V_k \in [v, v+h_2)\}/h_1 h_2$$

  - Mark-specific cumulative incidence functions:

$$F_k(t,v) = \lim_{h_2 \to 0} P\{T_k \leq t, V_k \in [v, v+h_2)\}/h_2$$

- The functions have a *crude* (not *net*) interpretation

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Hypothesis Testing

- Define $VE(t,v) = 1 - \frac{\lambda_1(t,v)}{\lambda_2(t,v)}; \quad VE(t) = 1 - \frac{\lambda_1(t)}{\lambda_2(t)}$
- Test

$$
\begin{aligned}
H_0 : VE(t,v) &= VE(t) \text{ for all } t \in [0,\tau] \\
&\text{versus} \\
H_1 : VE(t,v_1) &\leq VE(t,v_2) \text{ for all } v_1 \leq v_2, t \in [0,\tau] \\
H_2 : VE(t,v_1) &\neq VE(t,v_2) \text{ for some } v_1 \leq v_2, t \in [0,\tau]
\end{aligned}
$$

- $H_0 \Leftrightarrow \lambda_1(t,v)/\lambda_2(t,v)$ does not depend on v

Hypothesis Testing

- Define doubly cumulative mark-specific hazard functions

$$\Lambda_k(t,v) = \int_0^v \int_0^t \lambda_k(s,u)\, ds\, du, \qquad k = 1,2$$

- **Idea of testing procedures:** Compare a nonparametric estimate of $\Lambda_1(t,v) - \Lambda_2(t,v)$ with an estimate under H_0

Hypothesis Testing

- Nelson–Aalen-type estimator (Huang and Louis, 1998, Biometrika):

$$\widehat{\Lambda}_k(t,v) = \int_0^t \frac{N_k(ds,v)}{Y_k(s)},\ t \geq 0,\ v \in [0,1]$$

$$Y_k(t) = \sum_{i=1}^{n_k} I(X_{ki} \geq t)$$

$$N_k(t,v) = \sum_{i=1}^{n_k} I(X_{ki} \leq t, \delta_{ki} = 1, V_{ki} \leq v)$$

Hypothesis Testing

- H_0 holds $\Leftrightarrow$

$$\Lambda_1(t,v) = \int_0^t \frac{\lambda_1(s)}{\lambda_2(s)} \Lambda_2(ds,v)$$

- Under H_0, estimate $\Lambda_1(t,v) - \Lambda_2(t,v)$ by

$$\int_0^t \left[\frac{\widehat{\lambda}_1(s)}{\widehat{\lambda}_2(s)} - 1 \right] \widehat{\Lambda}_2(ds,v)$$

with

$$\widehat{\lambda}_k(t) = \frac{1}{b_k} \int_{u_1}^{u_2} K\left(\frac{t-s}{b_k} \right) d\widehat{\Lambda}_k(s)$$

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Test Process and Test Statistics

- **Test process:**

$$L_n(t,v) = \sqrt{\frac{n_1 n_2}{n}} \int_0^t H_n(s) \left[\widehat{\Lambda}_1(ds,v) - \frac{\widehat{\lambda}_1(s)}{\widehat{\lambda}_2(s)} \widehat{\Lambda}_2(ds,v) \right]$$

- **Test statistics:**

$$\widehat{U}_1 = \sup_{v_1<v_2} \sup_{0<t_1<t_2<\tau} \{L_n(t_2,v_2) - L_n(t_2,v_1) - L_n(t_1,v_2) + L_n(t_1,v_1)\}$$

$$\widehat{U}_2 = \sup_{0\le v\le 1} \sup_{0<t_1<t_2<\tau} |L_n(t_2,v) - L_n(t_1,v)|$$

Theoretical Properties

- **Theorem 1:** Under regularity conditions

$$L_n(t,v) \rightarrow^d L(t,v)$$

  in $D([0,\tau]\times[0,1])$ as $n \rightarrow \infty$

- $\Rightarrow$ Under $H_0, \hat{U}_1 \rightarrow^d U_1$ and $\hat{U}_2 \rightarrow^d U_2$
- Let $c_{1\alpha}$ and $c_{2\alpha}$ be the $(1-\alpha)$ quantile of U_1 and U_2
  - $P(\hat{U}_j > c_{j\alpha}) \rightarrow \alpha$ under H_0

Theoretical Properties

- **Theorem 2:** Under regularity conditions

$$P(\hat{U}_1 > c_{1\alpha}) \rightarrow 1 \text{ under } H_1$$
$$P(\hat{U}_2 > c_{2\alpha}) \rightarrow 1 \text{ under } H_2$$

- Critical values $c_{j\alpha}$ unknown and difficult to obtain
- $\Rightarrow$ Use a resampling procedure to approximate $c_{j\alpha}$

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Monte-Carlo Procedure

- Let $W_{1i} \sim N(0,1), i = 1, \cdots, n_1; W_{2i} \sim N(0,1), i = 1, \cdots, n_2$
- Define a simulated test process $\tilde{L}_n(t,v)$, a function of:
  - W_{1i}, W_{2i}
  - $\widehat{\lambda}_1(t), \widehat{\lambda}_2(t)$
  - A smooth estimate of $\Lambda_2'(t,v) = \frac{d}{ds}\Lambda_2(s,v)|_{s=t}$
- **Theorem 3:** Under regularity conditions, conditional on the observed data sequence

$$\tilde{L}_n(t,v) \rightarrow^d L(t,v)$$

in $D([0,\tau] \times [0,1])$ under H_0 as $n \rightarrow \infty$

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Monte-Carlo Procedure

- Acceptance/Rejection procedure:
  - Compute $\widehat{\tilde{U}}_1$ and $\widehat{\tilde{U}}_2$ based on $\tilde{L}_n(t,v)$
  - Based on B replicates $\widehat{\tilde{U}}_j$, compute

    $\widehat{c}_{j\alpha} = (1-\alpha)^{th}$ percentile of $\widehat{\tilde{U}}_{j1}, \cdots, \widehat{\tilde{U}}_{jB}$
  - Reject H_0 if $\widehat{U}_j > \widehat{c}_{j\alpha}$

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Estimation Procedure

- Sample size too small to reliably estimate

  $VE(t,v) = 1 - \frac{\lambda_1(t,v)}{\lambda_2(t,v)}$

- Alternatively, consider

$$\begin{aligned} VE(t,v) &= 1 - \frac{F_1(t,v)}{F_2(t,v)} \\ &= 1 - \lim_{h \to 0} \frac{P(T \leq t, V \in [v, v+h) | 1)}{P(T \leq t, V \in [v, v+h) | 2)} \end{aligned}$$

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Estimation Procedure

- Estimate $VE(t,v)$ by $1-\frac{\widehat{F}_1(t,v)}{\widehat{F}_2(t,v)}$, where

$$\widehat{F}_k(t,v)=\frac{1}{2b}\int_0^t \frac{\widehat{S}_k(s-)}{Y_k(s)}N_{vk}(ds)$$

$N_{vk}(t)=\sum_{i=1}^{n_k} I(X_i\le t,\delta_i=1,v-b<V_i\le v+b)$

$\widehat{S}_k(t)=$ Kaplan-Meier estimate of $S_k(t)$

- $\widehat{F}_k(t,v)=$ continuous analog of $\widehat{F}_{kj}(t)$ for a discrete mark j

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Estimation Procedure

- $Var\{\widehat{F}_k(t,v)\}$ can be estimated by

$$\frac{1}{(2b)^2}\int_0^t \left[\frac{\widehat{S}_k(s-)}{Y_k(s)}\right]^2 N_{vk}(ds)$$

- 95% pointwise confidence intervals:

$$\widehat{VE}(t,v) \pm 1.96 \times \widehat{Var}\{\widehat{VE}(t,v)\}^{1/2}$$

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Illustration

- First preventive HIV vaccine efficacy trial completed in February 2003
- AIDSVAX, a bivalent recombinant gp120 vaccine, developed and tested by VaxGen, Inc.
- Trial conducted in the U.S./Netherlands/Canada/Carribean, $n = 5403$, 2:1 randomization to vaccine:placebo
- Volunteers tested for HIV infection every 6 months for 3 years
- For HIV infected subjects, the gp120 region of HIV was sequenced

Results of Trial

- **Primary analysis:**

	Number Randomized	Number Infected	Percent Infected
Vaccine	3598	241	6.7%
Placebo	1805	127	7.0%

$$\widehat{VE} = 5.9\%, \quad 95\% \ CI \ \ (-16.7\%, 24.2\%), p = 0.58$$

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Sieve Analysis Illustration

- Define V as the percent mismatch in V1-V2-V3 of the infecting strain relative to the MN vaccine strain
- Two pseudo examples:

  1. (**null case**) Use the real failure times, indicators, and marks, and randomly permute the vaccination statuses to achieve $\approx$ 2:1 vaccine:placebo ratio

Sieve Analysis Illustration

2. (**alternative case**) Use the real failure times, indicators, and marks, and select the vaccination statuses such that

$$P(Z=1|V=v)=\frac{\exp\{\alpha+\beta v\}}{1+\exp\{\alpha+\beta v\}}$$

with α and β chosen such that $P(Z=1|V=\bar{V})=2/3$ and $P(Z=1|V=\max(V))=0.99$

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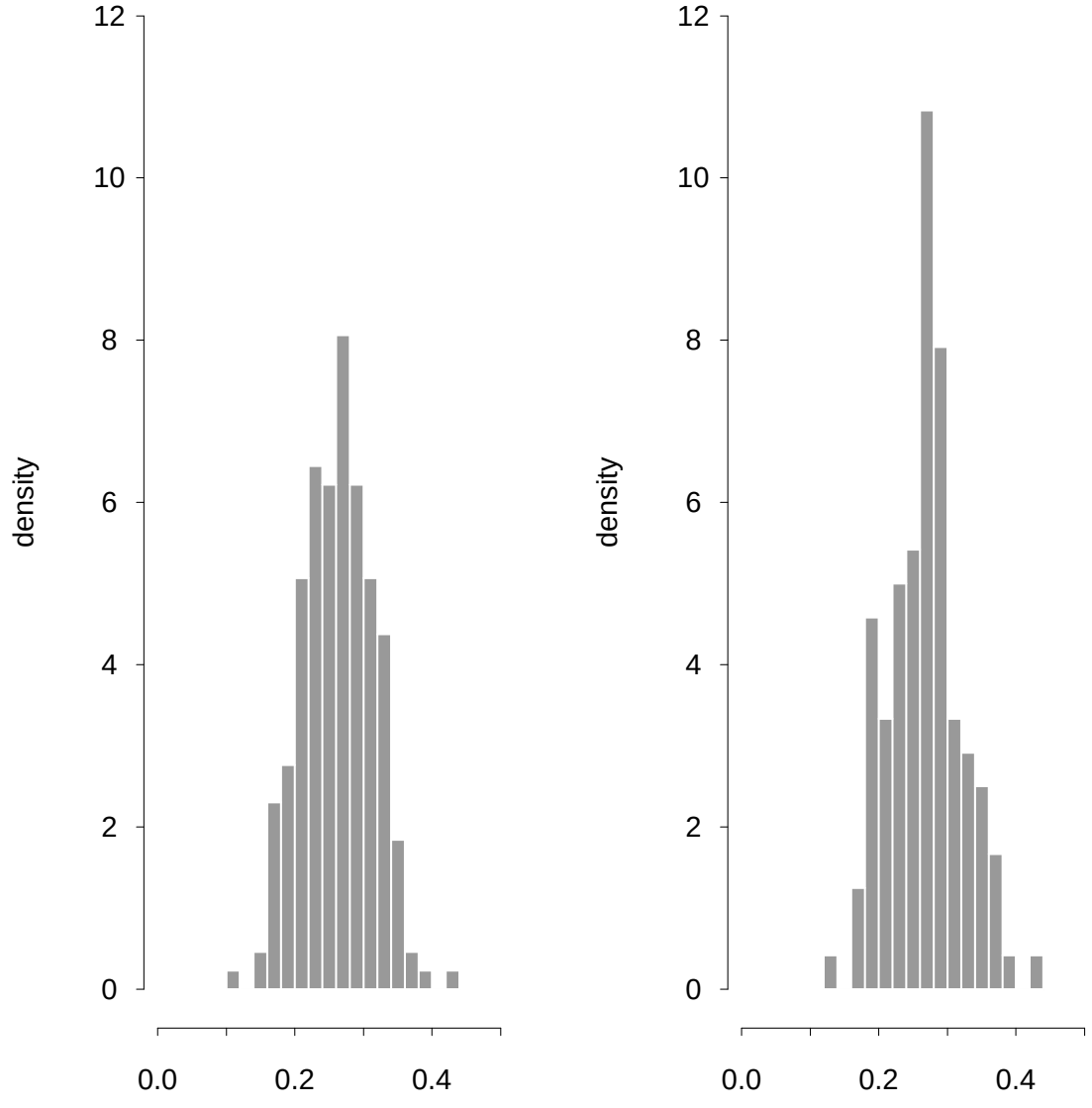
Example 1 (null case)

	n	mean	range
Vaccine	217	0.348	0.12-0.43
Placebo	120	0.335	0.14-0.44

Example 1 (null case)

Distributions of V1-V2-V3 Strain Distance



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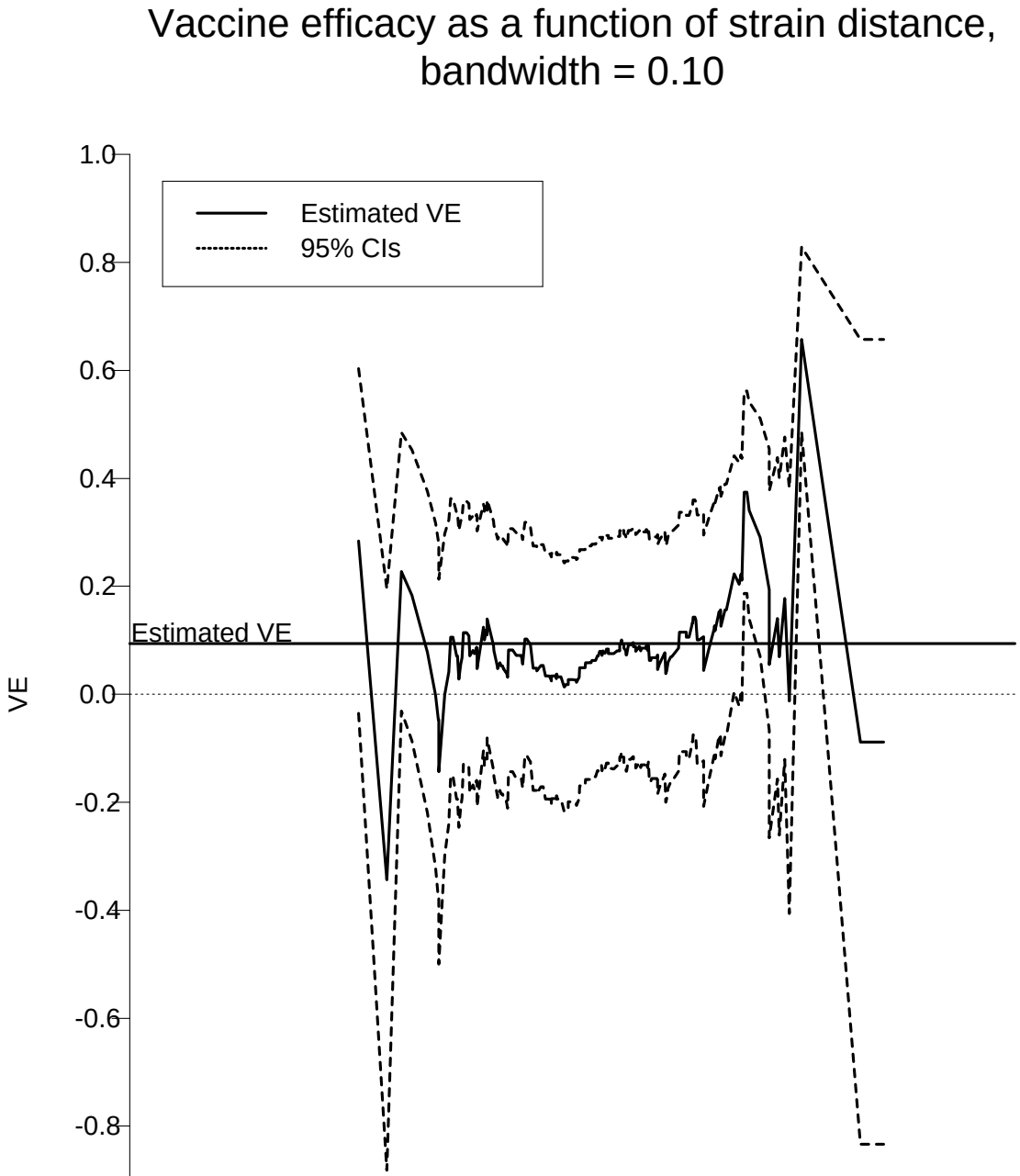
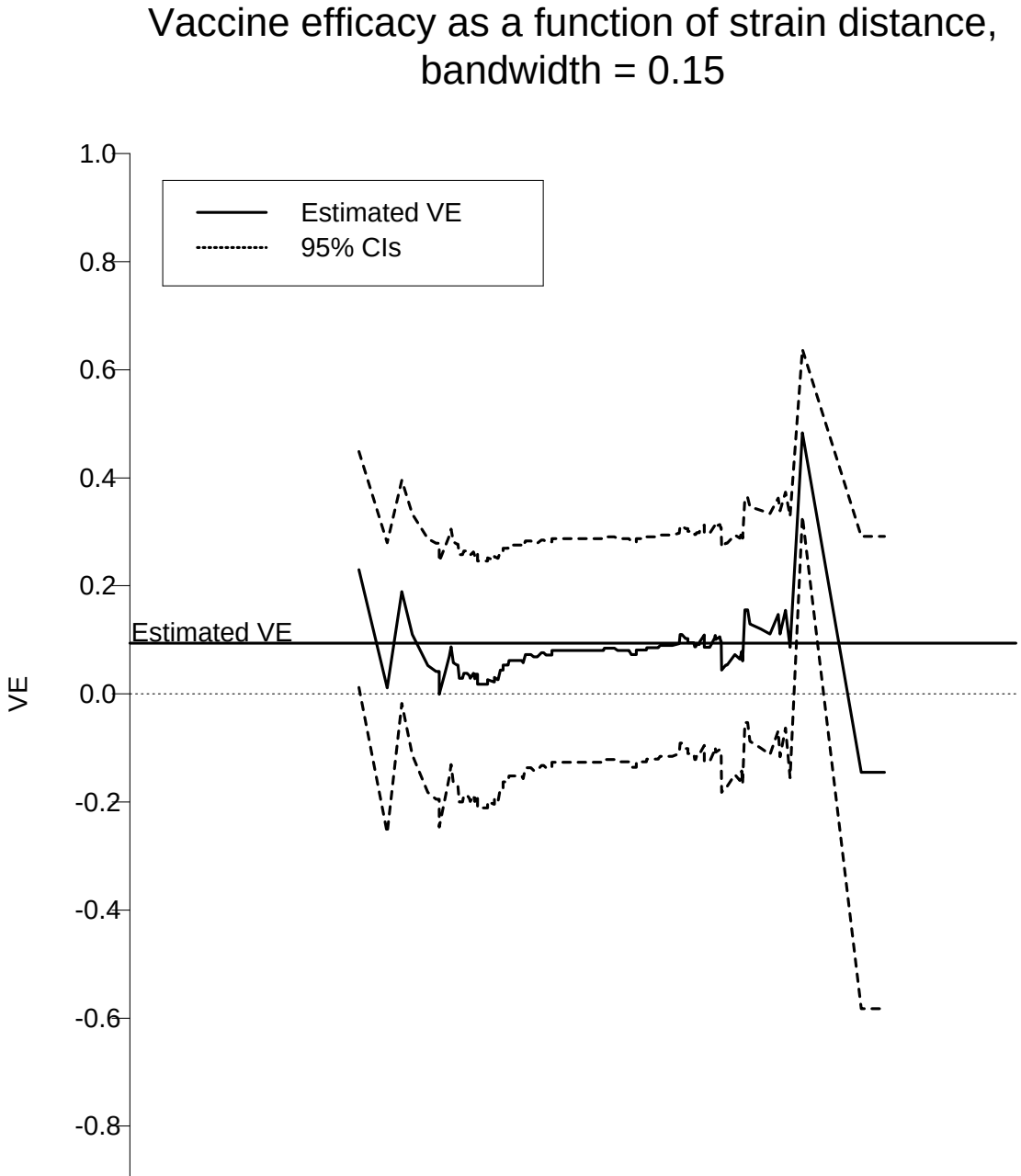
Example 1 (null case)

- Implementation of testing and estimation procedures:
  - Time range 2-36 months
  - bandwidth $= 8.5$ months
  - Distance range 0.12-0.44
  - bandwidth $= 0.10, 0.15, 0.20$
- $\tilde{U}_1 = 0.348, \tilde{U}_2 = 0.335$
  - Based on 1000 simulations, $p_1 = 0.677, p_2 = 0.523$

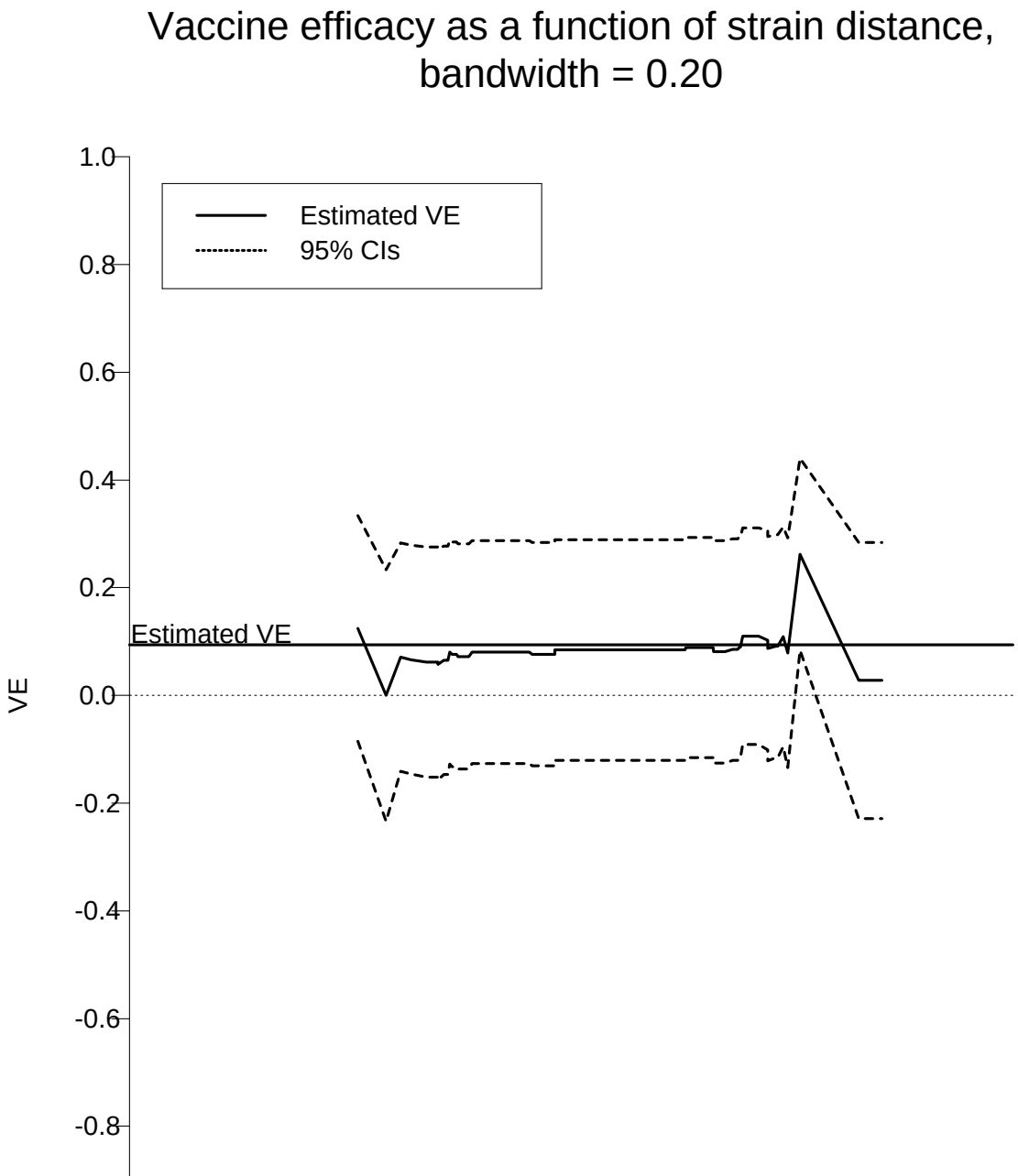
Example 1 (null case)



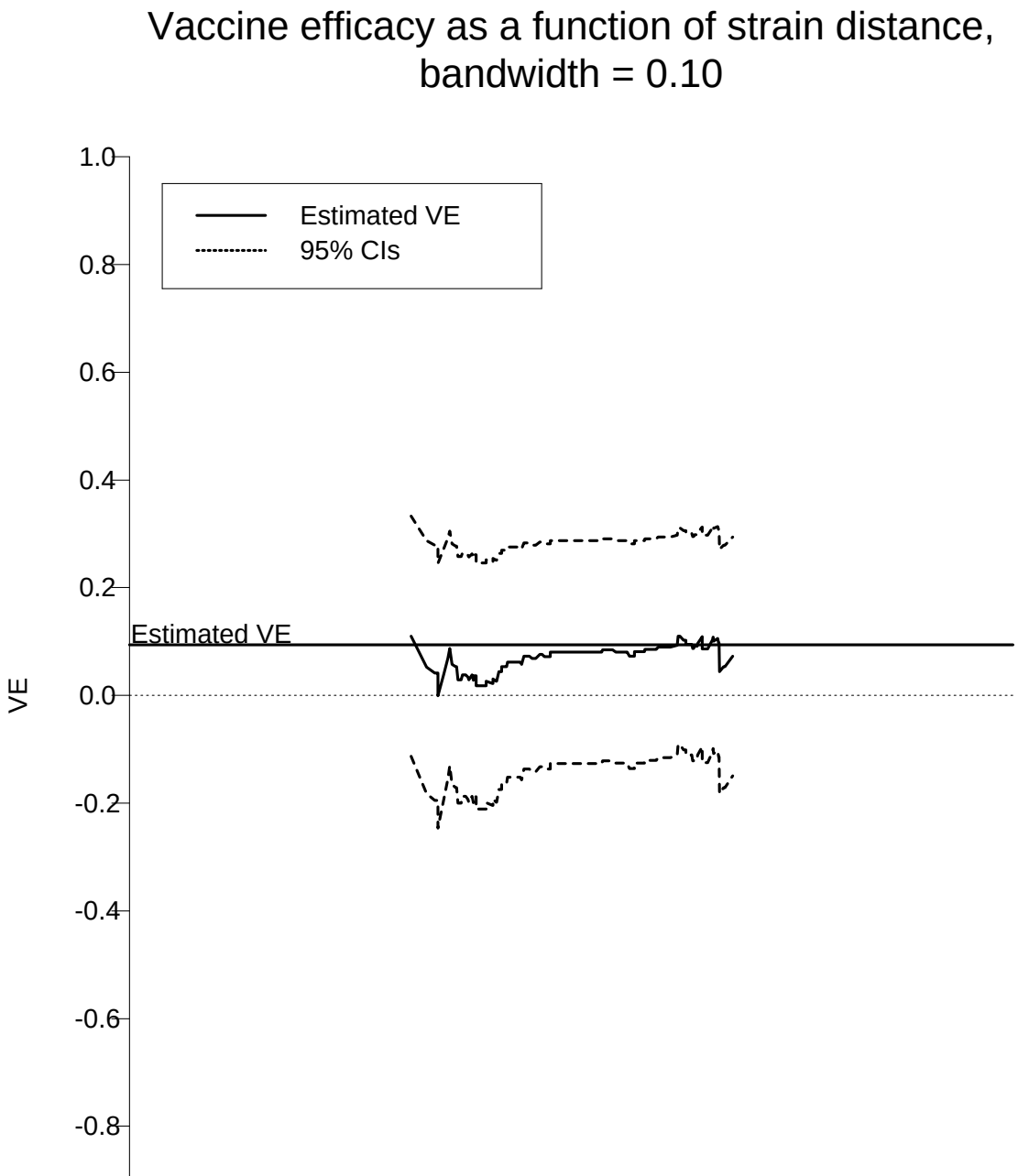
Example 1 (null case)



Example 1 (null case)



Example 1 (null case)



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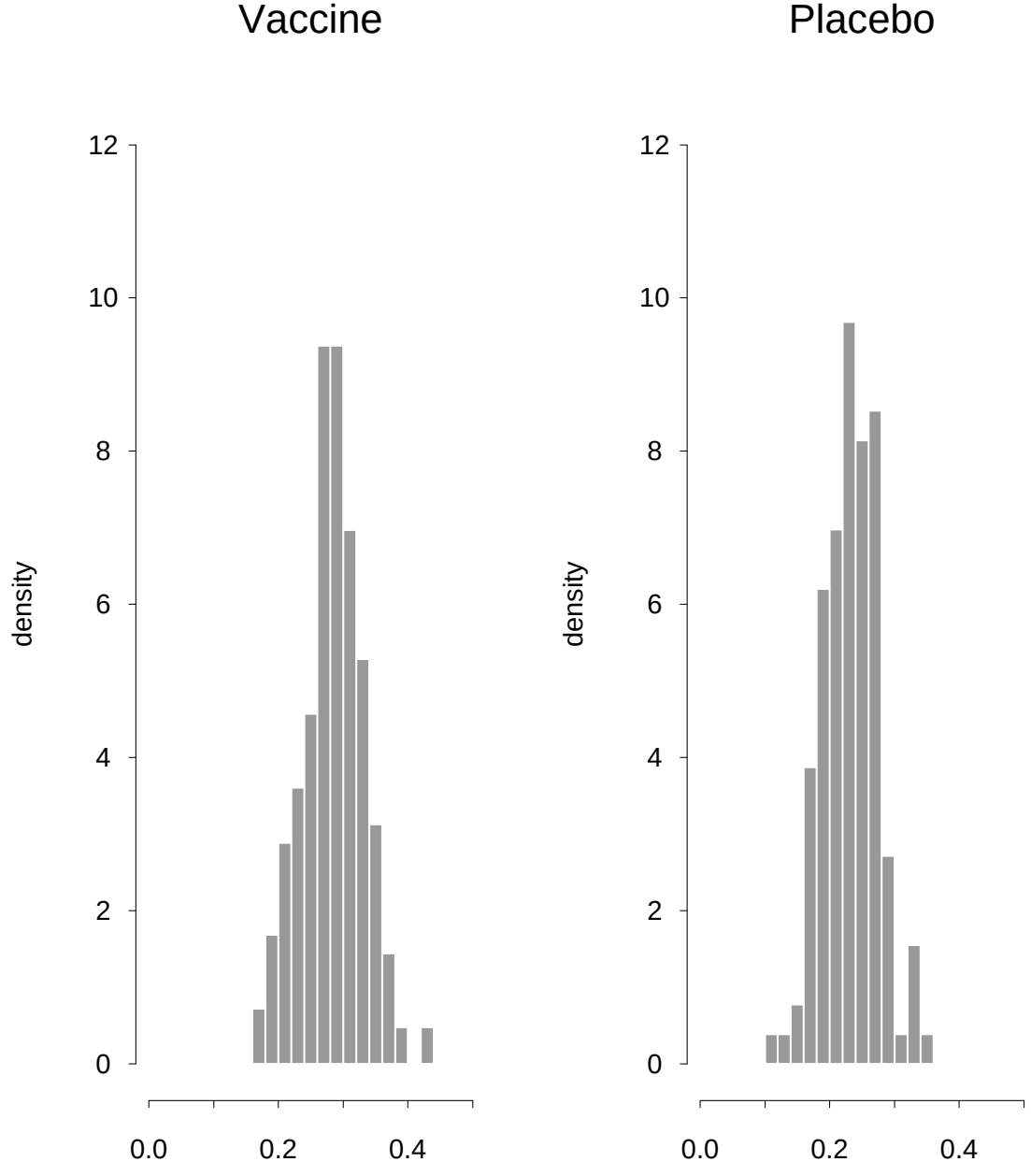
Example 2 (alternative case)

	n	mean	range
Vaccine	208	0.285	0.17-0.44
Placebo	129	0.232	0.12-0.34

Example 2 (alternative case)

Distributions of V1-V2-V3 Strain Distance



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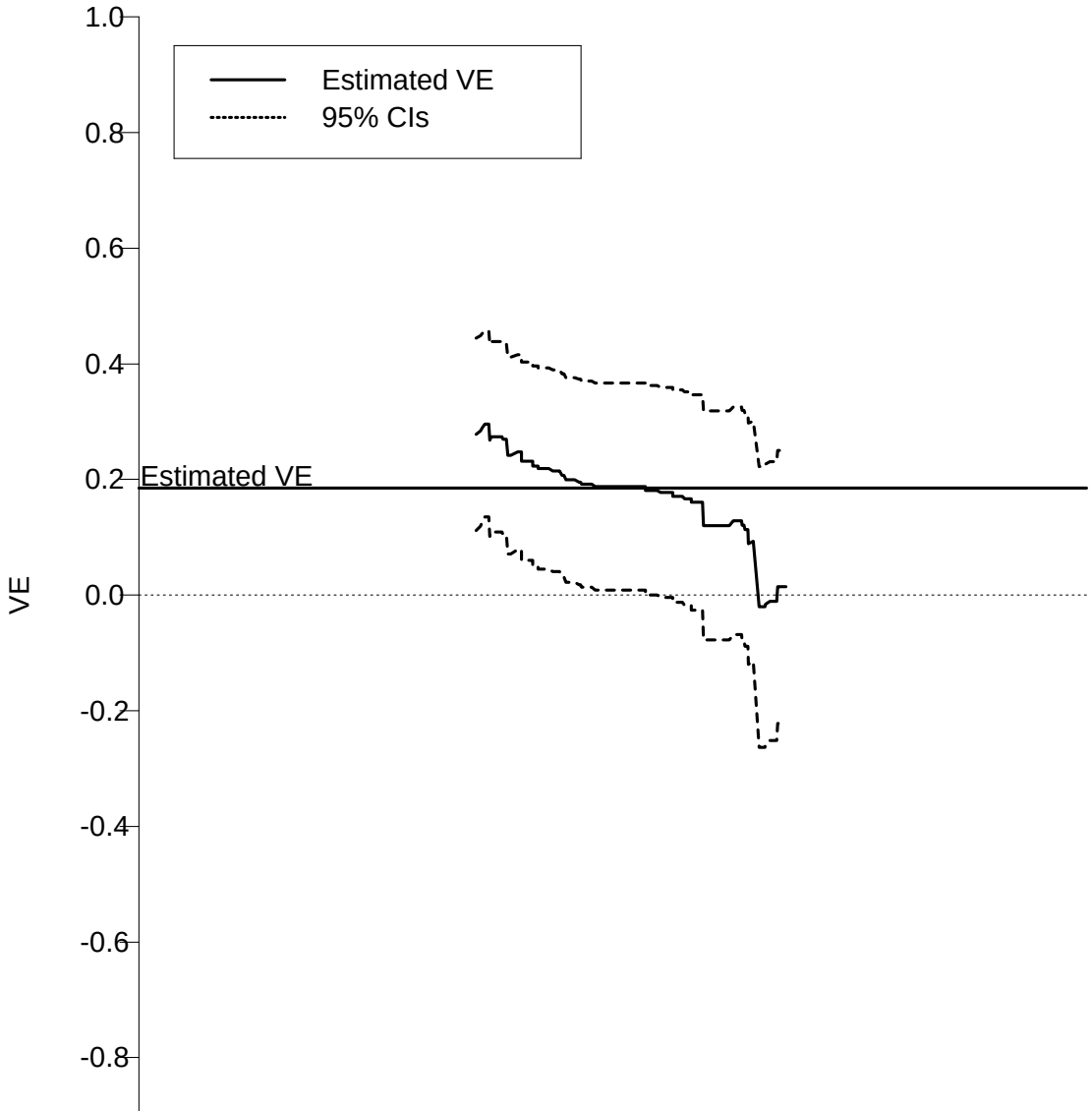
Example 2 (alternative case)

- Implementation of testing and estimation procedures:
  - Time range 2-36 months
  - bandwidth $= 8.5$ months
  - Distance range 0.15-0.35
  - bandwidth $= 0.15$
- $\tilde{U}_1 = 1.169, \tilde{U}_2 = 1.272$
  - Based on 1000 simulations, $p_1 < 0.001, p_2 < 0.001$

Example 2 (alternative case)

Vaccine efficacy as a function of strain distance,
bandwidth = 0.10



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Future Research

- Simultaneous confidence bands for $VE(t,v)$ in v for t fixed and in t for v fixed
- Study $VE(t,v)$ with covariate adjustment
  - Continuous mark-specific Cox regression model
- Causal inference/Sensitivity analysis to address the fundamental nonidentifiability problem for competing risks data
  - Principal stratification approach (Frangakis and Rubin, 2002, Biometrics)