Module 8: Evaluating Immune Correlates of Protection

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Session 10: Evaluating a Specific Surrogate of Protection

Outline of Session 10

- Part A: Comparing biomarkers and risk models as principal surrogate endpoints (Huang and Gilbert 2011)
- Part B: Sampling Design and Estimation (Huang, Gilbert, and Wolfson 2013)

Outline of Part A

- (I) the predictiveness curve technique for evaluating and comparing risk prediction models
- (II) evaluation of markers and models for principal surrogate effects

  — Summary measure

  — Semiparametric estimation method

Part A (I): The Predictiveness Curve

- Setting:

  Evaluate the capacity of a continuous marker S to predict the risk of a binary disease outcome Y, $Y = 0, 1$
- $Risk(S) = P(Y = 1|S)$
- $\rho = P(Y = 1)$
- Definition:

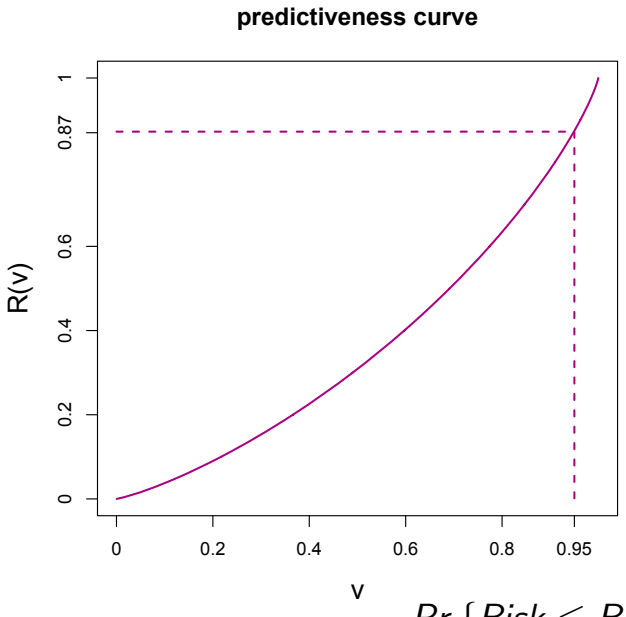
  "Predictiveness": the distribution of *Risk* in the population.

  How do we characterize the distribution of *Risk*?

The Predictiveness Curve

Definition:

- "Predictiveness curve": (Bura and Gastwirth 2001, Huang et al. 2007)
  — the *Risk*-quantile plot
  — the curve of $R(v)$ vs v, where $R(v)$ is the v^{th} quantile of *Risk* in the population, $v \in (0, 1)$,

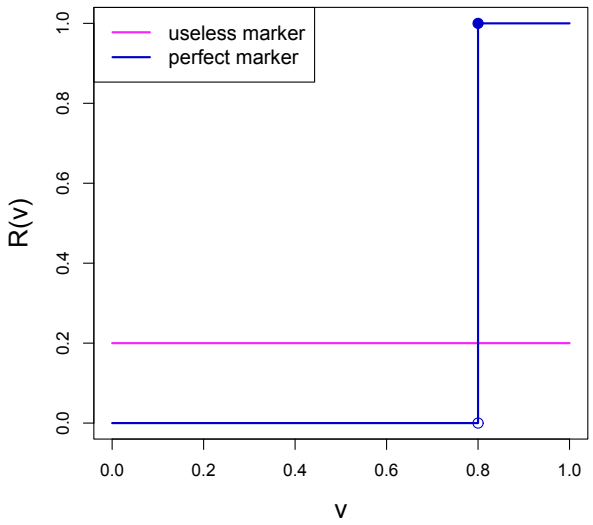


$$Pr\{Risk \leq R(v)\} = v$$

Predictiveness Curve (Cont.)

- Useless marker: horizontal line at $\rho = P(Y = 1)$
- Perfect marker:

$$Risk = \begin{cases} 0, & v \in (0, 1-\rho) \\ 1, & v \in (1-\rho, 1) \end{cases}$$



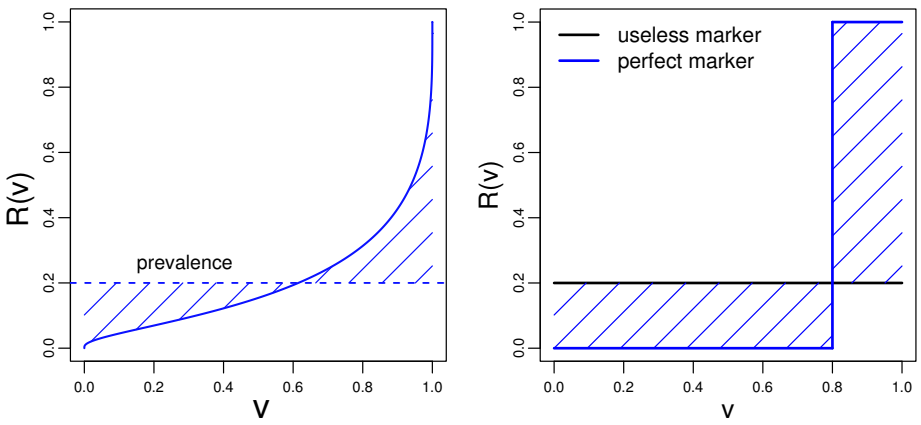
Properties of the Predictiveness Curve

- Area under the curve $= E[E(Y|S)] = P[Y = 1] \equiv \rho$
- Monotone increasing curve
- Provide a common scale to compare markers (or models): S could be multivariate
- Summary measure needed for comparison

Total Gain

$$\text{TG} = \int_0^1 |R(v) - \rho| dv \qquad \text{(Bura and Gastwirth 2001)}$$

- Useless marker: TG=0
- Perfect marker: TG=$2\rho(1-\rho)$



Total Gain (Cont.)

- For a risk threshold c,

  $Sensitivity(c) = P(Risk > c|Y = 1)$

  $1 - Specificity(c) = P(Risk > c|Y = 0)$

- Standardized TG

$$\frac{\text{TG}}{2\rho(1-\rho)} = \sup_c\{Sensitivity(c) + Specificity(c)\} - 1$$

  (Huang and Pepe 2009)

Estimation of The Predictiveness Curve Based on a Risk Model

- Fit the risk model (allow for large flexibility)

$$P(Y = 1|S) = G(\beta, S)$$

- Estimate the distribution of *Risk*

  (Huang & Pepe 2007, 2009)

Part A (II): Evaluation of the Principal Surrogate Endpoints

Thai Trial (2004-2009)

- Goal: assessing the efficacy of the ALVAC/AIDSVAX vaccine regimen on preventing HIV infection
- 16,395 HIV-seronegative participants 1:1 randomized to vaccine (ALVAC/AIDSVAX) or placebo
- Immune correlates (biomarkers): immunogenicity measured in case-control sample (at 1:5 ratio) at week 26 prior to HIV infection

  — Antibody binding to V1/V2 region, Neutralization antibody ...

Ouestion: can treatment effects on these biomarkers reliably predict treatment effects on the clinical endpoint?

Goals of Surrogates

Qin et al 2007, Gilbert et al 2008, 2011

- Ultimate Goal:

  Bridging/general surrogates: predict clinical treatment effect in a new setting (new population, new vaccine)
  — involves untestable assumptions
  — meta-analysis of multiple efficacy trials, phase IV post-licensure studies ... (Daniels and Hughs 1997; Molenberghs et al., 2008)
- First Step:

  Specific surrogates: predictions restricted to the same setting as current trial
  — statistical surrogate (Prentice 1989)
  — controlled natural direct and indirect effects
  — principal surrogate (particularly suitable for vaccine development) (Gilbert et al 2011)

Notation

Consider a randomized clinical trial

- Y: clinical endpoint, binary disease outcome
- Z: binary treatment indicator, $Z = 0, 1$
- S: candidate surrogate biomarker of interest
- W: baseline covariates, measured on everyone

Potential Outcome: for unit i, $Y_i(z)$, $S_i(z)$

Principal Surrogate

Based on a potential-outcomes framework, comparing

$$risk_{(1)}(s_1, s_0) \equiv P\{Y(1) = 1 | S(1) = s_1, S(0) = s_0\}$$

and

$$risk_{(0)}(s_1, s_0) \equiv P\{Y(0) = 1 | S(1) = s_1, S(0) = s_0\}$$

- Average Causal Necessity (ACN) (Frangakis and Rubin 2002, Gilbert and Hudgens 2008)
  $risk_{(1)}(s_1, s_0) = risk_{(0)}(s_1, s_0)$ for all fixed $s_1 = s_0$
- Average Causal Sufficiency (ACS) (Gilbert and Hudgens 2008)
  if $s_1 - s_0 > C$ for a threshold C, then
  $risk_{(1)}(s_1, s_0) < risk_{(0)}(s_1, s_0)$

Principal Surrogate Value

- For a univariate marker, ACN and ACS can be assessed (Gilbert and Hudgens 2008)
- Open question: quantify how valuable/reliable the biomarker is as a surrogate, and compare the surrogate value of different models

  — Compare markers

  — Evaluating a marker's incremental value

Generalization of the Predictiveness Curve

	Risk prediction markers	Surrogate markers
Binary outcome	Y	$Y(0) - Y(1)$, assuming $Y(0) \geq Y(1)$
	0: non-diseased 1: diseased	0: vaccine ineffective 1: vaccine effective
Variable of interest	$Risk(S)$ $= P(Y\|S)$	$risk_{(0)}\{S(1), S(0)\} - risk_{(1)}\{S(1), S(0)\}$ $= P\{Y(0) - Y(1)\|S(1), S(0)\}$

- The predictiveness curve $R(v)$ vs v, where $R(v)$ is the v^{th} quantile of $risk_{(0)}\{S(1), S(0)\} - risk_{(1)}\{S(1), S(0)\}$
- Area under the curve always equals to $\rho_0 - \rho_1 = P\{Y(0) = 1\} - P\{Y(1) = 1\}$

Standardized Total Gain

- For a threshold c,

  $Sensitivity(c) = P\{risk_{(0)} - risk_{(1)} > c | Y(0) - Y(1) = 1\}$

  $1 - Specificity(c) = P\{risk_{(0)} - risk_{(1)} > c | Y(0) - Y(1) = 0\}$

- $$\frac{\text{TG}}{2(\rho_0 - \rho_1)\{1 - (\rho_0 - \rho_1)\}} = \sup_c \{Sensitivity(c) + Specificity(c)\} - 1$$

  — if we use $risk_{(0)}\{S(1), S(0)\} - risk_{(1)}\{S(1), S(0)\}$ as a decision variable to classify a subject into the binary group $Y(0) = Y(1)$ or $Y(0) > Y(1)$

- Free of disease prevalence

Case CB

- Constant Biomarkers: $S_i(0) = c$ for all i for some constant c

  — take $c = 0$ when S is immune response to vaccine (Gilbert and Hudgens 2008)

- From now on, we omit $S(0)$ and use S to denote $S(1)$

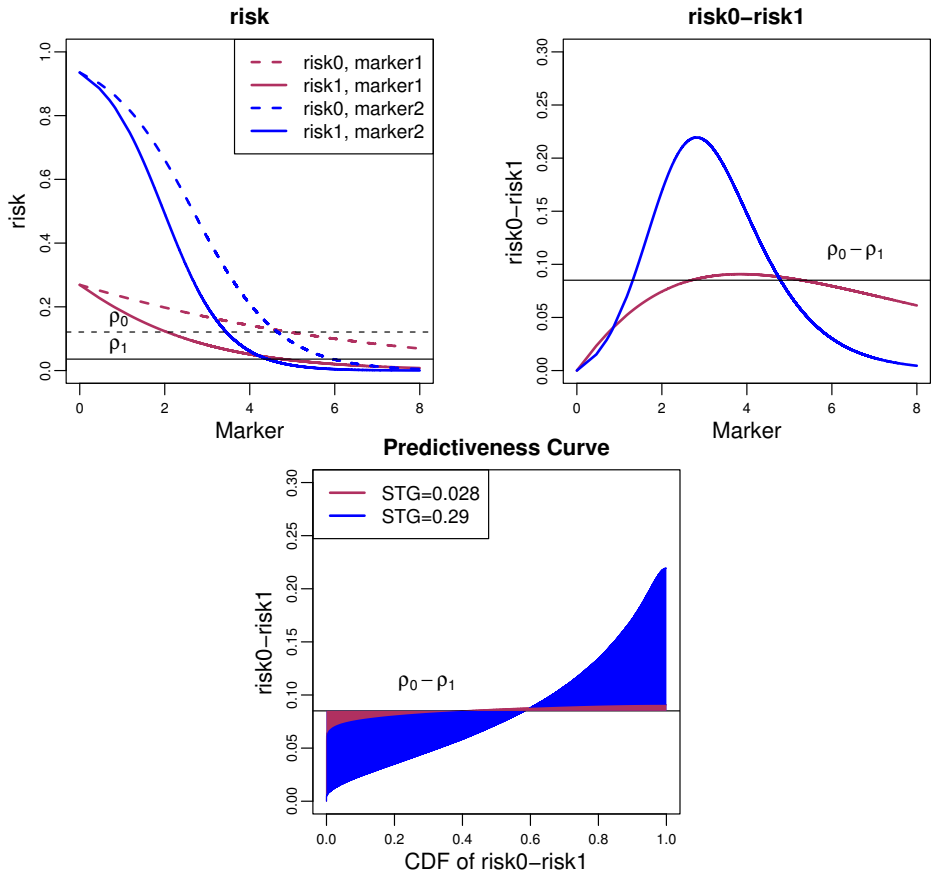


Figure: Comparing two markers.

Challenges for Surrogates Evaluation

- In a standard trial design, for subjects in placebo arm, we do not know what their immune responses would be if they receive vaccination instead

- Two ways have been proposed in Follmann 2006 for dealing with missing S

  — Use baseline predictor W to predict immune response (BIP)

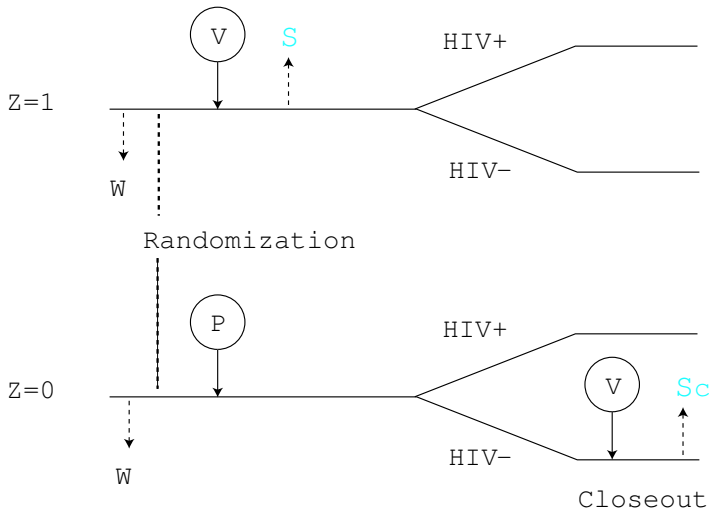
  — Augment the study design with a closeout placebo vaccination (CPV) component

Baseline Predictor Approach

- Utilize baseline predictors W that are correlated with S, such as immune responses to non-HIV vaccine
- Since $S(1)$ is missing in all placebo subjects, identifiability of the risk model with BIP only replies on untestable imposed constraint (Gilbert and Hudgens 2008)

Closeout Placebo Vaccination (CPV) (Review)

- Identifiability of risk model replies on *untestable* imposed constraint when $S(1)$ is missing in all placebo subjects
- CPV: a portion of placebo patients who are uninfected at the end of the trial receive vaccine at closeout and their immune response S_c is measured (Follmann 2006)



Closeout Placebo Vaccination (CPV)

- Under time constancy assumption, substitute closeout immune response S_c for $S(1)$
- Allows fully nonparametric estimation of risk conditional on S, Z, W (Follmann 2006)

$$\begin{aligned} & P\{Y(0)=1|S,W\} \\ = \; & 1 - \frac{P\{S|Y(0)=0,W\}\,[1-P\{Y(0)=1|W\}]}{P(S|W)} \end{aligned}$$

Assumptions

- Stable unit treatment value and Consistency:

  $S(1), S(0), Y(1), Y(0)$ for a subject are independent of the treatment assignments of other subjects

- Ignorable treatment assignments:

  $Z \perp W, S(1), S(0), Y(1), Y(0)$
  They imply that $\{S(1), S(0)|Z=1, W\}$ has the same distribution as $\{S(1), S(0)|Z=0, W\}$.

- Assumption: time constancy of immune response $S_c \stackrel{d}{=} S$

  — $S(1) = S^{true} + U_1$

  — $S_c = S^{true} + U_2$

  — U_1 and U_2 are iid

Conditional Likelihood

- Missing at random (by design)
- Let δ indicates availability of S, i.e. $S(1)$ or S^c, subject i's contribution to the likelihood

  1. $\delta_i = 1 : P(Y_i|Z_i, W_i, S_i)$
  2. $\delta_i = 0 : P(Y_i|Z_i, W_i) = \int P(Y_i|Z_i, s, W_i)dF(s|W_i)$,

  where F is joint CDF for S conditional on W.
- In a randomized trial, $\{S|Z = 1, W\}$ has the same distribution as $\{S|Z = 0, W\}$

Estimated Likelihood Approach

An estimated likelihood approach for dealing with missing data is natural in this scenario (Pepe and Fleming 1991)

- estimate distribution of S conditional on W based on a validation set in vaccine group

  — Obtain $\hat{F}(S|W)$
- estimate probability of Y conditional on Z and W, and enter that into the conditional likelihood

  — Maximize

  $\prod_{\delta_i=1} P(Y_i|Z_i, W_i, S_i) \prod_{\delta_i=0} \int P(Y_i|Z_i, s, W_i)d\hat{F}(s|W_i)$

Estimated Likelihood Approach

Gilbert and Hudgens 2008

- Fully parametric wrt $P(Y|Z, W, S)$ and $F(S|W)$
- Nonparametric: requiring discretized S and W

Semiparametric method (Huang and Gilbert 2011):

- Parametric $P(Y|Z, W, S)$
- Semiparametric location-scale model for $F(S|W)$

Estimation

- Semiparametric modeling approach for estimating a risk model
- Incorporate multiple biomarkers

Risk Model

Let $S_1, \ldots, S_J$ indicate potential marker values with vaccination for markers $j, j = 1, \ldots, J$

$$\begin{aligned} & risk_{(Z)}(S_1, \ldots, S_J, W) \\ = \; & P\{Y(Z) = 1 | S_1 = s_1, \ldots, S_J = s_J, W = w\} \\ = \; & g\left(\beta_0 + \beta_1 Z + \sum_{j=1}^{J} \beta_{2j} S_j + \sum_{j=1}^{J} \beta_{3j} S_j Z + \beta_4^T W\right) \end{aligned}$$

Modeling joint distribution of markers conditional on W

- Validation subset: n_V subjects in the vaccine group with $\delta = 1$
- Model $F(s_1, \ldots, s_J | W)$ semiparametrically
- Assuming for each j in $1, \ldots, J$, $S_j | W$ follows a location-scale model with mean and log-scale parameter being functions of W (Heagerty and Pepe 1999)

$$F(s_j | W) \sim F_{(j)}^{(0)}\left(\frac{s_j - \mu_j(W)}{\sigma_j(W)}\right) = F_{(j)}^{(0)}(\epsilon_j)$$

where $F_{(j)}^{(0)}$ are un-specified univariate baseline CDFs for residuals ϵ_j.

Modeling distribution of $S_1, \ldots, S_J$ conditional on W

- Suppose $\mu_j(W), \log\{\sigma_j(W)\}, j = 1, \ldots, J$ are parametric functions of W:

$$\mu_j(W) = \gamma_j' W, \qquad \log\{\sigma_j(W)\} = \eta_j' W$$

Estimating γ_j, η_j by solving estimating equations for mean and variance for S_j separately.

$$\sum_{i=1}^{n} \frac{W_i(Y_i - \gamma_j' W_i)}{\sigma_j^2(W_i)} = 0$$

$$\sum_{i=1}^{n} \frac{W_i[(Y_i - \gamma_j' W_i)^2 - \sigma_j^2(W_i)]}{\sigma_j^2(W_i)} = 0.$$

- Applying to the n_V subjects in the vaccinated group with $\delta = 1$ and obtain $\hat{\gamma}_j, \hat{\eta}_j$.
- For $j = 1, \ldots, J$, estimate

$$e_j = \frac{S_j - \hat{\gamma}_j'(W)}{\exp\{\hat{\eta}_j'(W)\}}.$$

Estimated Likelihood

- Obtain a series of pairs of residuals $(e_{1k}, \ldots, e_{Jk}), k = 1, \ldots, n_V$
- For subject i with $\delta_i = 0$, estimate

$P(Y_i = 1|Z_i, W_i) = \int risk_{(Z_i)}(s_1, \ldots, s_J, W_i) dF(s_1, \ldots, s_J|W_i)$ with

$$\frac{1}{n_V} \sum_{k=1}^{n_V} risk_{(Z_i)}\left(S_1 = S_{i1k}^{\star}, \ldots, S_J = S_{iJk}^{\star}, W_i\right)$$

where $S_{ijk}^{\star} = \hat{\gamma}_j' W_i + \exp(\hat{\eta}_j' W_i) e_{jk}, j = 1, \ldots, J; k = 1, \ldots, n_V$.

- Entering this into the likelihood,

$$\begin{aligned} & L(\beta; Y, Z, S_1, \ldots, S_J, W, \delta) \\ = & \prod_{i:\delta_i=1} P(Y_i|Z_i, S_{i1}, \ldots, S_{iJ}, W_i) \prod_{i:\delta_i=0} \hat{P}(Y_i|Z_i, W_i) \end{aligned}$$

Approximated Score Equations

Let

$$U(Y|Z, S_1, \ldots, S_J, W) = \frac{\partial \log\{P(Y|Z, S_1, \ldots, S_J, W)\}}{\partial \beta}$$

The score for a subject i with $\delta = 0$ is:

$$\begin{aligned} & \frac{\partial \log\{P(Y_i|Z_i, W_i)\}}{\partial \beta} \\ = \quad & \frac{\int U(Y_i|Z_i, s_1, \ldots, s_J, W_i) P(Y_i|Z_i, s_1, \ldots, s_J, W_i) P(s_1, \ldots, s_J|W_i) ds_1 \ldots s_J}{\int P(Y_i|Z_i, s_1, \ldots, s_J, W_i) P(s_1, \ldots, s_J|W_i) ds_1 \ldots s_J}, \end{aligned}$$

which can be approximated by

$$\sum_{k=1}^{n_V} \frac{U(Y_j|Z_j, S^\star_{i1k}, \ldots, S^\star_{iJk}, W_i) P(Y_i|Z_i, S^\star_{i1k}, \ldots, S^\star_{iJk}, W_i)}{\sum_{k=1}^{n_V} P(Y_i|Z_i, S^\star_{i1k}, \ldots, S^\star_{iJk}, W_i)},$$

where $S^\star_{ijk} = \hat{\gamma}_j' W_i + \exp(\hat{\eta}_j' W_i) e_{jk}$.

Algorithm

1. Apply semiparametric location-scale model to subjects in the validation set
2. Start with an initial estimate of β
3. Use the units with $\delta = 1$ as they are. For each i with $\delta_j = 0$, construct a set of filled-in data, $\{Y_i, S^\star_{i1k}, \ldots, S^\star_{iJk}, Z_i, W_i\}, k = 1, \ldots, n_V$.
4. For each filled-in observation $\{Y_j, S^\star_{i1k}, \ldots, S^\star_{iJk}, Z_i, W_i\}, k = 1, \ldots, n_V$, calculate an associated weight,
$$w_{jk} = \frac{P(Y_1|S^\star_{i1k}, \ldots, S^\star_{iJk}, Z_i, W_i)}{\sum_{k=1}^{n_V} P(Y_i|S^\star_{i1k}, S^\star_{iJk}, Z_i, W_i)}$$
5. Fit a weighted GLM to the augmented dataset and obtain a new estimate of β
6. Repeat steps 3 to 5 till convergence

Estimation of Standardized Total Gain

Given a W of interest, for $k = 1, \ldots, n_V$, compute

$S^\star_{jk} = \hat{\gamma}_j' W + \exp(\hat{\eta}_j' W) e_{jk}, j = 1, \ldots, J,$

- For randomly sampled $S_1, \ldots, S_J$ from vaccine arm

$$\begin{aligned} \hat{\rho}_z &= \frac{1}{n_V} \sum \widehat{risk}_{(z)}(S^\star_{1k}, \ldots, S^\star_{Jk}, W) \\ \widehat{\mathrm{TG}} &= \frac{1}{n_V} \sum \left| \widehat{risk}_{(0)}(S^\star_{1k}, \ldots, S^\star_{Jk}, W) - \widehat{risk}_{(1)}(S^\star_{1k}, \ldots, S^\star_{Jk}, W) - \{\hat{\rho}_0 - \hat{\rho}_1\} \right| \end{aligned}$$

- Inverse probability weighting (IPW) to account for biased sampling

Simulation

- 3000 subjects, 1:1 randomized to placebo and vaccinated
- groups
- $$\begin{pmatrix} S_1 \\ S_2 \\ W \end{pmatrix} \sim N\left\{ \begin{pmatrix} 3 \\ 3 \\ 3 \end{pmatrix}, \begin{pmatrix} 1 & \rho_{ss} & \rho_{sw} \\ \rho_{ss} & 1 & \rho_{sw} \\ \rho_{sw} & \rho_{sw} & 1 \end{pmatrix} \right\}$$

$$\begin{aligned} & risk_{(Z)}(S_1, S_2, W) \\ = \; & \mathrm{logit}\left(\beta_0 + \beta_1 Z + \beta_2 S_1 + \beta_3 S_1 Z + \beta_4 S_2 + \beta_5 S_2 Z + \beta_6 W\right), \end{aligned}$$

such that $P(Y = 1|Z = 1) = 0.06$, $P(Y = 1|Z = 0) = 0.12$.

- Assume all subjects in vaccinated group and all uninfected subjects in placebo group have S_1, S_2 measured

Table: Performance of the estimators for risk model parameters.
One-marker model:
$risk_{(Z)}(S_1, W) = \Phi(\gamma_0 + \gamma_1 Z + \gamma_2 S_1 + \gamma_3 S_1 Z + \gamma_4 W + \gamma_5 WZ)$.

		Parameter					
		One-marker model					
	n	γ_0	γ_1	γ_2	γ_3	γ_4	γ_5
		2.12	-0.60	-0.80	-0.094	-0.49	0.093
Bias	500	0.17	-0.04	-0.07	0.003	-0.04	0.02
	1000	0.07	0.003	-0.03	-0.01	-0.02	0.01
	3000	0.034	-0.02	-0.018	0.01	-0.003	-2e-4
SE	500	1.00	1.20	0.54	0.60	0.22	0.31
	1000	0.62	0.75	0.33	0.37	0.14	0.21
	3000	0.34	0.43	0.18	0.20	0.08	0.11
Cover*	500	92.37	93.95	92.87	93.86	92.77	95.24
	1000	92.85	94.45	93.38	93.98	93.32	94.18
	3000	93.60	93.52	93.77	94.75	93.85	94.59

*Coverage of 95% bootstrap percentile confidence interval

Table: Performance of the estimators for risk model parameters.
Two-marker model: $risk_{(Z)}(S_1, S_2, W) =$
$\Phi(\beta_0 + \beta_1 Z + \beta_2 S_1 + \beta_3 S_1 Z + \beta_4 S_2 + \beta_5 S_2 Z + \beta_6 W + \beta_7 WZ)$.

		Two-marker model							
	n	β_0	β_1	β_2	β_3	β_4	β_5	β_6	β_7
		3.04	-0.40	-0.40	-0.05	-0.90	-0.25	-0.40	0.12
bias	500	0.42	-0.03	-0.06	0.01	-0.14	-0.04	-0.06	0.03
	1000	0.19	-0.01	-0.03	-0.003	-0.06	-0.01	-0.03	0.01
	3000	0.08	-0.04	-0.02	0.01	-0.02	0.005	-0.004	0.001
SE	500	1.41	1.79	0.59	0.68	0.69	0.84	0.27	0.40
	1000	0.86	1.08	0.39	0.44	0.43	0.52	0.16	0.24
	3000	0.43	0.54	0.2	0.23	0.22	0.26	0.09	0.13
Cover*	500	91.39	94.15	94.46	95.28	94.46	94.97	91.49	95.28
	1000	92.76	94.5	93.70	94.17	92.56	93.36	92.82	93.76
	3000	93.93	94.34	94.09	94.67	93.52	94.18	93.52	94.59

*Coverage of 95% bootstrap percentile confidence interval

Table: Performance of the semiparametric estimator for estimating TG and STG.

		One-marker model				Two-marker model			
		W=1.72		W=3.00		W=1.72		W=3.00	
	n	TG	STG	TG	STG	TG	STG	TG	STG
		0.053	0.206	0.032	0.388	0.08	0.313	0.043	0.517
Bias	500	0.02	0.08	0.002	0.05	0.04	0.15	0.01	0.13
	1000	0.01	0.03	-8e-4	0.01	0.02	0.08	0.01	0.07
	3000	0.002	0.01	1.2e-5	0.005	0.01	0.03	0.001	0.02
SE	500	0.04	14.95	0.02	4.66	0.04	1.81	0.02	22.38
	1000	0.03	0.21	0.02	0.29	0.03	0.13	0.02	0.75
	3000	0.02	0.08	0.01	0.11	0.02	0.06	0.01	0.07
Cover*	500	92.37	95.74	95.14	97.52	81.23	87.59	92.51	93.23
	1000	95.86	96.19	94.39	96.79	88.4	87.59	93.7	94.3
	3000	95.11	94.92	93.48	94.72	91.33	90.03	93.74	93.35

*: Coverage of 95% bootstrap percentile confidence interval
Note $P(Y = 1|Z = 0, W)$ and $P(Y = 1|Z = 1, W)$ are 0.31 and 0.16 at $W = 1.72$ and 0.075 and 0.032 at $W = 3.0$.

Table: Performance of the semiparametric estimators to detect a higher TG and STG with a two-marker model compared with a one-marker model.

		W=1.7		W=3.0	
	n	TG diff	STG diff	TG diff	STG diff
		0.027	0.107	0.011	0.129
Bias	500	0.01	0.03	0.003	0.04
	1000	0.01	0.03	0.002	0.03
	3000	0.002	0.01	3e-4	0.004
SE	500	0.04	15.7	0.02	23.1
	1000	0.03	0.14	0.01	0.82
	3000	0.02	0.06	0.01	0.09
Cover*	500	97.72	99.28	98.76	97.1
	1000	97.24	97.98	96.3	96.97
	3000	96.09	96.61	93.87	93.87

*Coverage of 95% bootstrap percentile confidence interval

Conclusion

- Identifying risk difference as a function of marker values allows us to use the predictiveness curve methodology to evaluate multiple surrogate markers together
- Total gain is a clinically meaningful summary measure of the corresponding predictiveness curve
- Semiparametric estimated-likelihood method provides a relatively robust way of estimating principal surrogate value of multiple markers

Conclusion and Discussion

- Generalize to other designs where W only measured in a subcohort sample (e.g. a case-control sample)

  — use only the subcohort data, weighted likelihood
- More general settings: when CB does not hold, assuming time-constancy at baseline and marker measurement, use S at baseline to substitute $S(0)$
- Optimization of sampling scheme

Part B

Sampling Design Optimization and Estimation for Evaluating Principal Surrogate Markers in HIV Vaccine Trials

Outline of Part B

- Surrogates of Protection in HIV vaccine trials
  - — Characterization of surrogate effects
  - — Limitation of existing design
- Design and Estimation for evaluating surrogates
- Optimize sampling scheme for immune assays

Surrogates of Protection

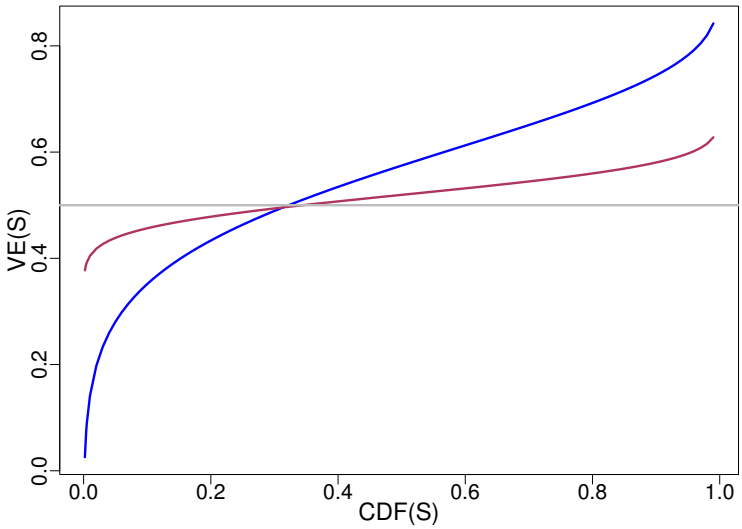
- Existing HIV vaccine does not have sufficient efficacy to warrant licensure
- Vaccine in RV144 Thai Trial achieved 30% efficacy (Rerks-Ngarm et al. 2009)
- Finding immune biomarkers such as T-cell responses and antibody binding levels are important for vaccine development
- Summary measures to characterize surrogate effect

  — vaccine efficacy curve

  — predicted population average effect of a refined vaccine
- HIV vaccine trials only enroll subjects without previous infectious with the pathogen: $S(0)$ is zero for all subjects, use S to denote $S(1)$

Vaccine Efficacy Curve

Curve of $VE(S)$ versus S (or CDF of S) provides a way to compare the ability of different immune responses to predict VE in the current setting



Goal: develop refined vaccine regimens that induce high levels of that biomarker in a larger percentage of vaccine recipients

Bridging to a New Vaccine

- Let Z^{new} denote a refined vaccine with potential marker value $S(1)^{new}$

- It is interesting to predict

  $CE^{new} = P(Y = 1|Z^{new} = 0) - P(Y = 1|Z^{new} = 1)$

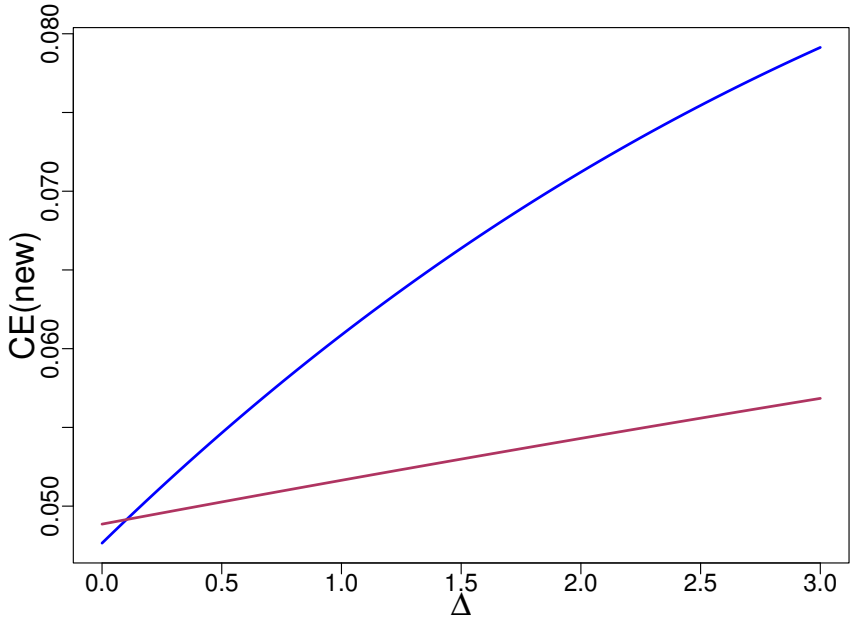
  based on information about $risk_{(Z)}(S)$ and $S(1)^{new}$

- How good this prediction is depends on:

  — Performance of the specific surrogate marker in the current setting

  — Our understanding about the biological mechanism of the surrogate and vaccine

Plot of CE^{new} versus Δ (the location shift in $S(1)^{new}$ relative to $S(1)$)



$$P[Y = 1|Z = z, S(1) = s] = g(\beta_0 + \beta_1 z + \beta_2 s + \beta_3 sz)$$

$$\Rightarrow \quad P[Y = 1|Z^{new} = z, S(1) = s] = g\{\beta_0 + \beta_1 z + \beta_2 s + \beta_3 (s + \Delta) z\}$$

Strategies for Estimating Prinicipal Surrogate Effects

- Use baseline predictor W to predict immune response (BIP)

  — Important for efficiency

- Augment the study design with a closeout placebo vaccination (CPV) component

  — Important for testing risk model assumptions

Model

$$P\{Y(Z)=1|S,W)\}=g(\beta_0+\beta_1 Z+\beta_2 S+\beta_3 SZ+\beta_4^T W+\beta_5^T WZ).$$

Existing Methods (Review)

An estimated likelihood approach (Pepe and Fleming 1991) for maximizing

$$\prod_{\delta_i=1} P(Y_i|Z_i,S_i,W_i)\prod_{\delta_i=0}\int P(Y_i|Z_i,s,W_i)dF(s|W_i),$$

where δ indicates whether $S(1)$ or S^c is available.

- estimate $\hat{F}(S|W)$: distribution of S conditional on W based on a validation set in vaccine group

  (Gilbert and Hudgens 2008; Wolfson and Gilbert 2009; Huang and Gilbert 2011)

- estimate probability of Y conditional on Z and W, and enter that into the conditional likelihood, maximize $\prod_{\delta_i=1} P(Y_i|Z_i,W_i,S_i)\prod_{\delta_i=0}\int P(Y_i|Z_i,s,W_i)d\hat{F}(s|W_i)$

Plan of the South Africa Trial

Gilbert, P.B., Grove, D., Gabriel, E., Huang, Y., Gray, G., Hammer, S. M., Buchbinder, S.P., Kublin, J., Corey, L., Self, S.G. (2011) A Sequential Phase 2b Trial Design for Evaluating Vaccine Efficacy and Immune Correlates for Multiple HIV Vaccine Regimens. *Statistical Communications in Infectious Diseases*.

- Simultaneously evaluate multiple prime/boost vaccine regimens against a shared placebo group
- Use sequential monitoring to evaluate efficacy and durability for each vaccine regimen
- Evaluation of the vaccine efficacy curve is being planned as a secondary objective

CPV Design (cont.)

Estimated likelihood method can be applied with or without CPV

When CPV is used, consider case-control sampling in the second phase

- IPW: use validation sample in vaccine arm only for estimating $F(S(1)|W)$ since $P(\delta = 1|Z = 0, Y = 1) = 0$
- incorporate CPV sample in the risk model

Following the notation in Follmann (2006), we consider the following two designs

— BIP: using baseline covariate (W) to predict S

— BIP + CPV

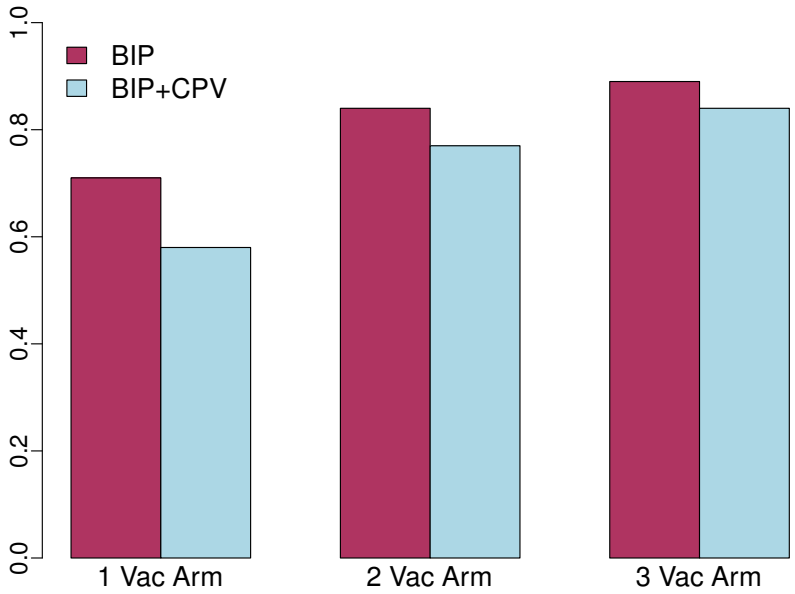


Figure: Power for testing $\beta_3 = 0$

$risk_{(Z)} = \Phi(\beta_0 + \beta_1 Z + \beta_2 S + \beta_3 SZ)$; VE(0)=0% and VE(4)=90%

Results show that the design without CPV is more powerful?

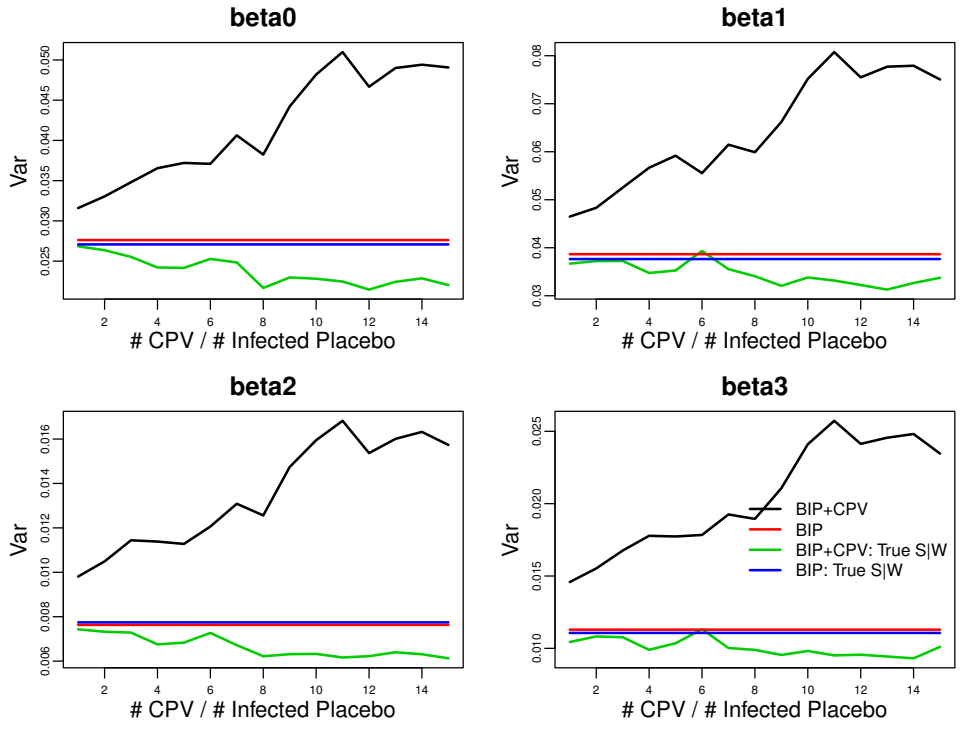


Figure: Variance of risk model parameter estimators from parametric estimated likelihood method. X-axis is ratio of CPV samples relative to infected placebos

- Counter-intuitive findings based on estimated likelihood approach seem to result from using two different sets of data in marker distribution estimation and risk model estimation in the BIP+CPV design

  — samples with $\delta = 1$ contribute to $P(Y|Z, W, S)$ in the conditional likelihood

  — samples with $\delta = 1$ and $Z = 1$ are used in estimating $F(S|W)$

- Would a method that incorporates CPV in marker distribution estimation help?

A Pseudo-Score Type Estimator

$$U(\beta, F) = \frac{\partial l(\beta, F)}{\partial \beta} = \sum_{\delta_i=1} U_\beta(Y_i|S_i, Z_i, W_j) + \sum_{\delta_j=0} U_\beta(Y_j|Z_j, W_j),$$

where

$$\begin{aligned} U_\beta(Y_j|Z_j, W_j) &= \frac{\int U_\beta(Y_j|s, Z_j, W_j) f_\beta(Y_j|s, Z_j, W_j) dF(s|W_j)}{\int f_\beta(Y_j|s, Z_j, W_j) dF(s|W_j)} \\ &= \frac{\int U_\beta(Y_j|s, Z_j, W_j) \frac{f_\beta(Y_j|s,Z_j,W_j)}{P(\delta=1|s,W_j)} dF(s|W_j, \delta = 1)}{\int \frac{f_\beta(Y_j|s,Z_j,W_j)}{P(\delta=1|s,W_j)} dF(s|W_j, \delta = 1)} \end{aligned}$$

From Bayes' theorem

$$dF(S|W) = \frac{dF(S|W, \delta = 1)P(\delta = 1|W)}{P(\delta = 1|S, W)}$$

A Pseudo-Score Type Estimator (Cont.)

To construct the pseudo-score, estimate

— $F(S|W, \delta = 1)$

— $P(\delta = 1|S, W) = \int \int P(\delta = 1|y, z, S, W) f_\beta(y|S, z, W) f(z) dydz$

Huang, Gilbert, Wolfson 2013, extending the work of Chatterjee, Chen, Breslow 2003

Consider the validation set to be the set used for accommodating the estimation of $S|W$,

The PS method can be applied to

— BIP design

— BIP+CPV design, with either vaccine samples or vaccine + CPV samples as the validation set

— requires $P(\delta = 1|S, W) > 0$

Simulation Studies

(S, W^*) bivariate normal with correlation $\rho = 0.5$
W: discretizing W^* by quartiles
$P(Y|S, Z, W) = \Phi(\beta_0 + \beta_1 Z + \beta_2 S + \beta_3 SZ)$

Study Design:

- Phase 1: $n = 4,000$ subjects 1:1 randomized to $Z = 0, 1$ arms, with W, Z, Y measured
- Phase 2: S measured, Bernoulli sampling stratified by Z, Y

  All cases with $Z = 1$ sampled; a portion of controls with $Z = 1$ and controls with $Z = 0$ sampled to achieve
- Parameters are chosen such that infection rate is 0.12 and 0.06 in $Z = 0$ and $Z = 1$ arm respectively

Pseudo-Score Estimator (PS) with Empirical Likelihood Estimator (EL)

Sampling ratio vs infected vaccinees		
Vaccine controls	Placebo controls (CPV)	Efficiency*
1	0	1.08
5	0	0.99
1	1	1.36
5	5	1.08
1	2	1.72

Efficiency*: $\frac{\text{var}(EL)}{\text{var}(PS)}$

Asymptotic Property for Pseudo-score Estimator

- The pseudo-score estimator is asymptotically normally distributed

$$\sqrt{N}(\hat{\beta}_{ps} - \beta) = -\Psi_{\beta}^{-1} \frac{1}{\sqrt{N}} \sum_{i=1}^{N} \phi(R_i, Y_i, S_i, Z_i, W_i) + o_p(1),$$

with variance contributed by estimating

1. β as a MLE
2. $S|W, \delta = 1$
3. $P(\delta = 1|Y, Z, W)$

Optimization of Marker Sampling Scheme

- Given limited resource in measuring $S(1)$, how to divide the samples between treatment arms
- Suppose we sample all cases in vaccine arm, varying the percent of non-infected samples between vaccine and placebo arms
- Plot asymptotic efficiency of PS estimator for % controls allocated to vaccine arm relative to the design where equal number of controls are sampled between vaccine and placebo arms

Optimization of Marker Sampling Scheme (Cont.)

Parameters of interest

- $\beta_0, \beta_1, \beta_2, \beta_3$

  $risk_{(Z)} = \Phi(\beta_0 + \beta_1 Z + \beta_2 S + \beta_3 SZ)$

- $VE(90\%)$: $VE(S)$ for S being 90^{th} percentile

- CE^{new}: predicted CE^{new} for a refined vaccine with true CE^{new}=75%

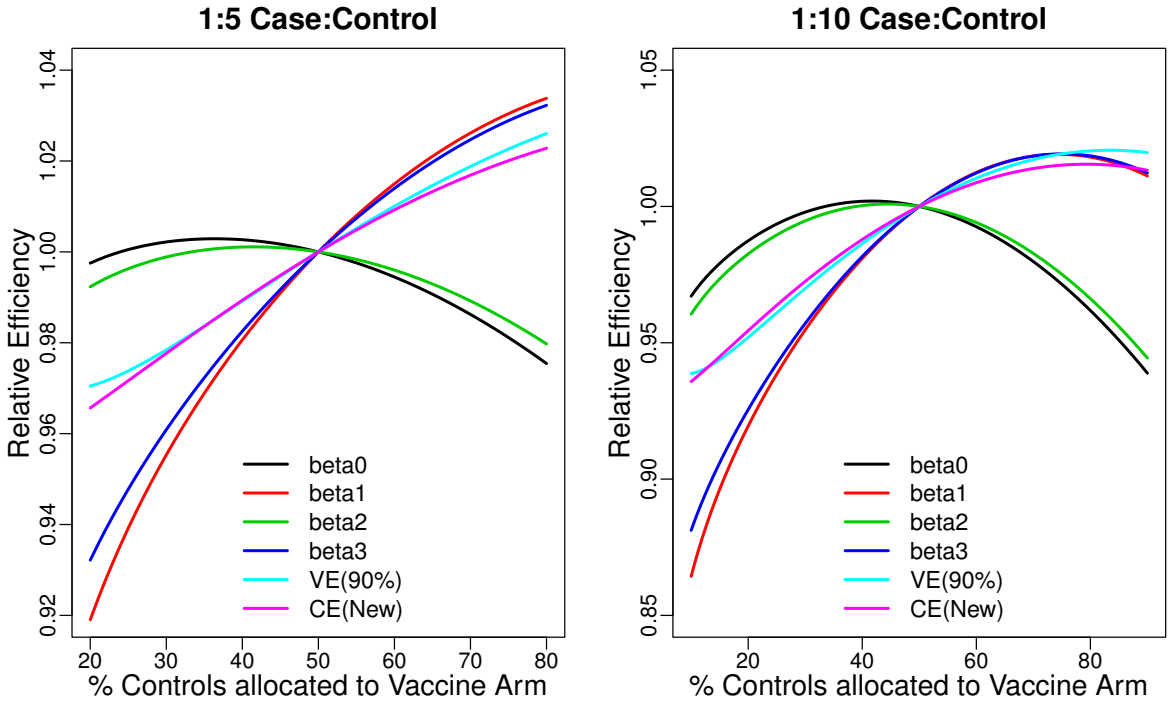
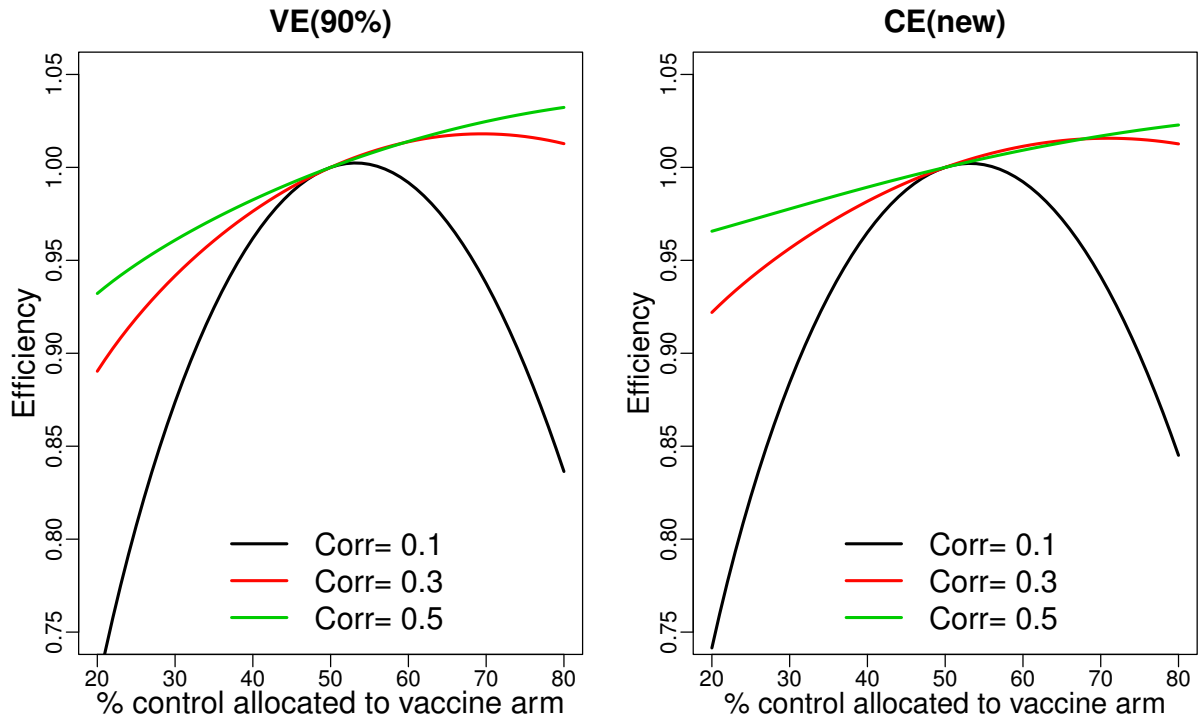


Figure: Efficiency relative to the design where equal numbers of controls have biomarker measured between vaccine and placebo arms; $Cor(S, W) = 0.5$.

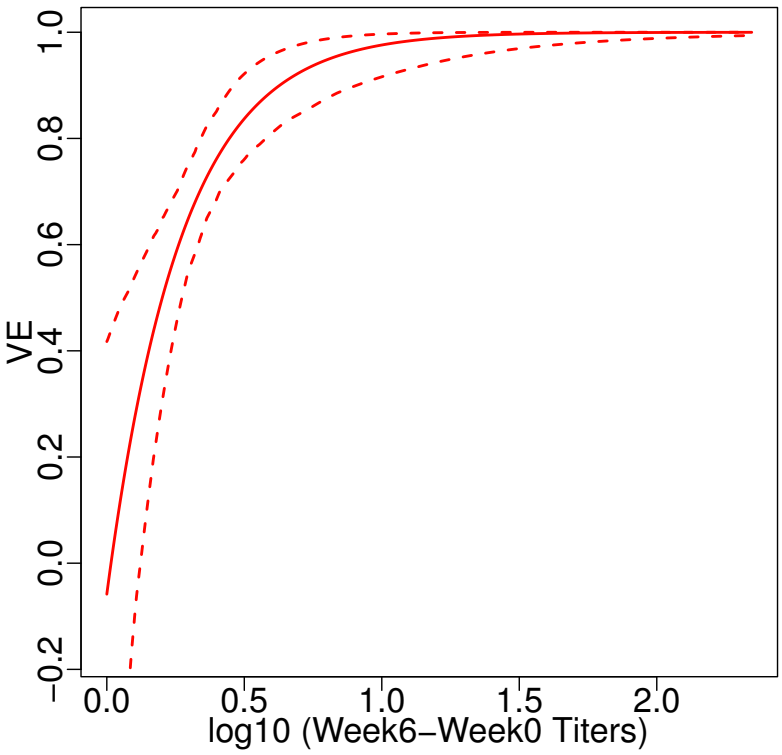


Sub-Sampling of Baseline Predictors (Ongoing Work)

- In RV144 Thai Trial, characteristics such as patients demographics and risk behavior are poorly correlated with immune response
- We target lab assay for candidates of future baseline predictor
  — immune response to tetanus and HBV vaccine
  — non-vaccination BIP
- Sub-sampling of baseline predictor is warranted for estimating vaccine efficacy in a cost-effective manner

Correlates of Protection for Herpes-Zoster Vaccine

- 22439 subjects 1:1 randomized to receive either the HZ vaccine or a placebo, VE=69.8% for preventing HZ (Schmader et al. 2012)
- $\simeq$2400 subjects have gpELISA antibody titers measured at baseline and week six after vaccination



Plan of the Research Trial in South Africa

Three arms with two primary vaccine regimens:

- 1700 receiving a vaccine regimen with NYVAC and protein
- 1700 receiving a vaccine regimen with DNA, NYVAC, protein
- 1700 placebo recipients

For vaccine regimen(s) that shows positive efficacy over 18 months, surrogates of protection with be assessed

Plan of the Research Trial in South Africa

- We will use BIP and possibly CPV approaches
  — a fraction of subjects will have baseline predictors measured (e.g. immune responses to tetanus and/or HBV vaccines)
  — all infected vaccinees and a fraction of uninfected vaccinees will have HIV vaccine-induced immune responses measured
  — a fraction of uninfected placebo recipients at the end of the trial will possibly receive vaccination and have HIV vaccine-induced immune responses measured

- Pseudo-score approach will be used to estimate the vaccine efficacy curve

- More investigations needed to determine the cost-effective sampling scheme (fraction, stratification) for measuring BIP and potential surrogates

Summary

- Plan to use the BIP + CPV design with subsampling of W in future efficacy trials; CPV is crucial because it allows estimating VE curves without relying on unverifiable assumptions
- When CPV samples is not available, sensitivity analysis is needed for partial identifiability
- Future work involves optimization of sampling design for W and S, and selection of covariates as risk predictors and/or baseline predictors