Module 8
Evaluating Immunological
Correlates of Protection

Session 9
Validation Using Prentice Criteria and Causal Inference Framework, Design Considerations

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Correlate of Protection (CoP)
(Plotkin and Gilbert, CID 2012)

- CoP is an immune marker statistically correlated with vaccine efficacy (predictive of vaccine efficacy)
  - CoP is *mechanistic* if immune response is a causal agent to protection
  - CoP is *non-mechanistic* if immune response predicts vaccine efficacy but is not a causal agent to protection

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A Classical Method For Evaluating Surrogate Endpoints - Prentice's criteria

Prentice (1989) established 4 criteria:

1. Show treatment effect on disease endpoint
2. Show treatment effect on surrogate endpoint (immune marker)
3. Show surrogate endpoint correlates with disease endpoint
4. Show that probability of disease is independent of treatment status, given the surrogate endpoint
   - full treatment effect captured by surrogate endpoint

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Validation of Surrogate of Protection Using Prentice's Criteria

Two Examples

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Pertussis Vaccine Example

Validation of Correlate of Protection using Prentice's Criteria

Storsaeter et al, Vaccine 1998;
Kohberger et al, Vaccine 2008

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Sweden Pertussis Vaccine Trials

- Sweden Trial I compared 3 pertussis vaccines and a placebo using DT vaccine (N=2100 to 2500 per group)
  - $DTaP_{2Bel}$ (SKB)
  - $DTaP_{5Can}$ (Sanofi-Pasteur)
  - DTwP (Sanofi-Pasteur)
  - DT (Swedish NBL)
- Efficacy and serology testing evaluated in a subset of 309 subjects after household exposure to *Bordetella pertussis*
- Logistic regression model developed for correlate of protection
  - Validation using Prentice's criteria

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Sweden Pertussis Vaccine Trials

- Sweden Trial II compared 4 candidate vaccines (no placebo was included)
  - $DTaP_{2Bel}$ (SKB)
  - $DTaP_{3Ita}$ (Novartis)
  - $DTaP_{5Can}$ (Sanofi-Pasteur)
  - DTwP (Evans Medical)
- Model developed from Trial I was applied to Trial II to predict relative efficacy
- Independent validation by comparing model predicted and observed efficacy

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Criterion 1: Vaccine Efficacy Sweden Trial I

Clinical definition	Exposed in DTPa2 group $N = 76$ Cases (cult pos)	VE% (95% CI)	Exposed in DTPa5 group $N = 86$ Cases (cult pos)	VE% (95% CI)	Exposed in DTPwc group $N = 57$ Cases (cult pos)	VE% (95% CI)	Exposed in DT group $N = 74$ Cases (cult pos)	Total no. of cases (cult pos)
Cough 1 day or more and positive lab criteria	61 (26)	5.7 (−9.1–19.6)	28 (13)	61.8 (47.4–72.2)	47 (25)	3.1 (−12.9–16.8)	63 (43)	199 (107)
Cough 8 days or more and positive lab criteria	58 (24)	10.4 (−4.4–23.1)	26 (12)	64.5 (50.4–74.6)	46 (25)	5.2 (−10.6–18.8)	63 (43)	193 (104)
Cough 21 days or more and positive lab criteria	35 (17)	43.2 (25.8–56.5)	21 (11)	69.9 (55.6–79.6)	37 (22)	19.9 (1.6–35.3)	60 (43)	153 (93)
Cough 30 days or more and positive lab criteria	29 (15)	44.6 (23.4–60.0)	14 (10)	76.4 (60.9–85.7)	34 (21)	13.5 (−12.5–33.5)	51 (37)	128 (83)
Spasmodic cough 21 days or more	29 (17)	42.4 (19.9–58.5)	14 (10)	75.4 (59.2–85.2)	27 (18)	28.5 (1.6–48.0)	49 (36)	119 (81)

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Criterion 2: Immune responses Sweden Trial I

Assay	Vaccine	No. of samples	1 month after dose 3 (32 days)	
IgG anti-PT	DTPa2	164	59.3	53.6–65.7
	DTPa5	170	49.8	45.0–55.1
	DTPwc	119	1.9	1.5–2.4
	DT	139	0.9	0.8–1.1
IgG anti-FHA	DTPa2	164	111.4	100.5–123.6
	DTPa5	170	33.3	30.0–37.1
	DTPwc	119	8.8	7.4–10.6
	DT	139	0.8	0.7–0.9
IgG anti-FIM 2/3	DTPa2	164	0.9	0.8–1.0
	DTPa5	170	352.4	304.1–408.3
	DTPwc	119	15.5	9.9–24.1
	DT	139	0.9	0.8–1.0
IgG anti-pertactin	DTPa2	164	0.6	0.6–0.7
	DTPa5	170	116.7	102.8–132.4
	DTPwc	119	12.6	9.7–16.4
	DT	139	0.6	0.6–0.7

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Model Development for Criterion 3

- Preexposure antibody titers measured by pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), fimbriae (FIM) 2/3
- Antibody titers were classified as ‘Low’ (<5 ELISA units) and ‘High’ (≥5)
- Logistic regression model:

$$P(\text{disease}) = \frac{1}{1+\exp(-y)}$$

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Model Development

- Results of logistic regression model:

$$P(\text{disease}) = \frac{1}{1+\exp(-y)}$$

$$y = 0.675 - 1.12\text{PT} - 1.992\text{FIM} - 1.589\text{PRN} + 1.993(\text{PT} \times \text{FIM})$$

- Variables are coded as 0/1 for low/High titers
- FHA antibody was not a significant factor in the model

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Proportion of Effect Explained (PE)

- Proportion of treatment effect explained by antibody was assessed by fitting two models:

$$\text{Model 1}: y = a_1 + b_1 \times \text{treatment}$$

$$\text{Model 2}: y = a_2 + b_2 \times \text{treatment} + \text{g(PT, FIM, PRN)}$$

where g( ) is the correlates model

$$\text{PE} = 1 - b_2 / b_1$$

- Result: treatment not significant given correlates (P=0.82)
- PE = 1 – 0.045/0.688 = 0.93 (95% CI: 0.51, 1.84)

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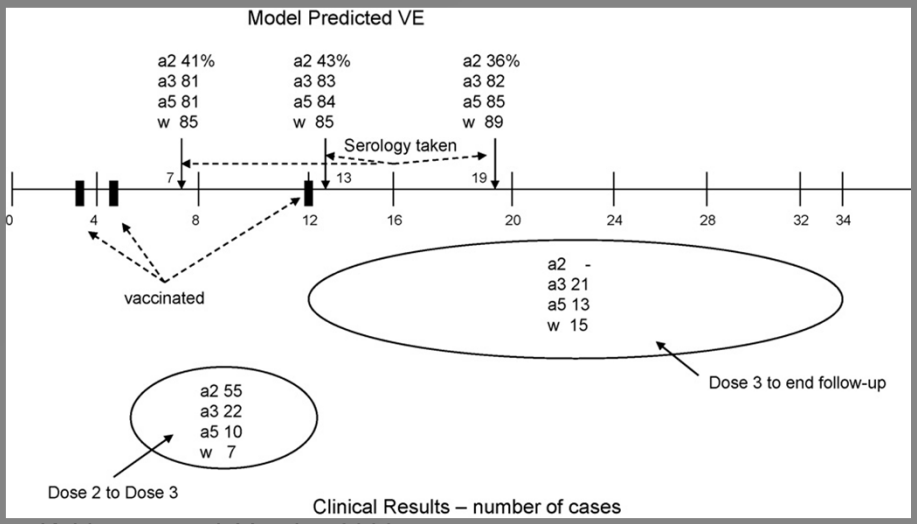
Independent Validation Using Data From Sweden Trial II



Kohberger et al, Vaccine 2008

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Independent Validation Using Data From Sweden Trial II

- Predicted VE for $DTaP_{2Bel}$ (a2) is 36-43% and VE for other vaccines is 81-89%
- Predicted number of cases for $DTaP_{2Bel}$ to be 3-6 fold higher than with other vaccines
  - Close to the actual case ratio of 2.5 to 7.8

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How to calculate the ratio of predicted number of cases?

$$\mathrm{VE}_1 = 1 - \frac{p_{v1}}{p_c} \Rightarrow p_c = \frac{1-\mathrm{VE}_1}{p_{v1}}$$

$$\mathrm{VE}_2 = 1 - \frac{p_{v2}}{p_c} \Rightarrow p_c = \frac{1-\mathrm{VE}_2}{p_{v2}}$$

$$\frac{1-\mathrm{VE}_1}{p_{v1}} = \frac{1-\mathrm{VE}_2}{p_{v2}} \Rightarrow \frac{p_{v1}}{p_{v2}} = \frac{1-\mathrm{VE}_1}{1-\mathrm{VE}_2}$$

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Herpes Zoster Vaccine Example (2 studies)

ZOSTAVAX®

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Study 1: Shingles Prevention Study
(Oxman *et al*., NEJM 2005)

- N = 38,546 subjects ≥60 years of age randomized 1:1 to receive ZOSTAVAX® or placebo
  - A substudy of N=1395 for immunogenicity
- Average of 3.1 years of HZ surveillance and ≥6-month follow-up of HZ pain after HZ rash onset
- Conducted by Dept. of Veteran Affairs (VA) in collaboration with the National Institutes of Health (NIH) and Merck & Co., Inc.

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Immunogenicity Substudy

- 1395 subjects at 2 study sites
  - Both efficacy and immunogenicity measures collected
- Antibody responses by glycoprotein enzyme-linked immunosorbent assay (gpELISA)
- Cell-mediated immune responses by
  - IFN-γ enzyme-linked immunospot assay (ELISPOT)
  - Responder cell frequency (RCF)

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Key Efficacy Endpoints of SPS

- HZ incidence
- Postherpetic neuralgia (PHN)
  - Clinically significant pain persisting for or present after 90 days of HZ rash onset
- HZ pain burden of illness (BOI)
  - Composite of incidence, severity, and duration of pain (Chang, Guess and Heyse 1994)
- Success requires VE lower bound > 25% for each endpoint

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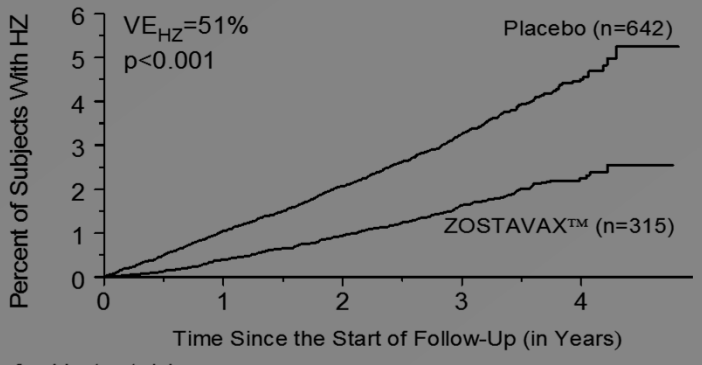
ZOSTAVAX® Efficacy: HZ Incidence

Estimate of the Cumulative Incidence of HZ Over Time by Vaccination Group



Number of subjects at risk

ZOSTAVAX™	19254	18994	18626	9942	1906
Placebo	19247	18915	18422	9806	1856

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Assessing Immunological Correlates of Protection

- Criterion 1: Vaccine is effective on clinical outcomes:
  Efficacy against HZ = 51%

- Criterion 2: Vaccine is effective in boosting the immune responses (substudy N=1395)
  - Antibody responses by gpELISA: 1.7 fold, $p<0.001$
  - T-cell responses by ELISPOT: 2.0 fold, $p<0.001$
  - T-cell responses by RCF: 1.9 fold, $p<0.001$

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SPS Immunogenicity Results

- ZOSTAVAX™ induced VZV-specific immune responses at 6 weeks postvaccination

	Geometric Mean Response (N = 691)		
	Day 0	Week 6	Fold Rise
gpELISA (units/mL)	278.8	474.7	1.7 (95% CI: 1.6, 1.8)
IFN-γ ELISPOT ($SFC/10^6$ PBMC†)	34.5	72.0	2.0 (95% CI: 1.8, 2.3)
RCF (responder cells/10^5 PBMC)	5.7	9.7	1.7 (95% CI: 1.6, 1.8)

† Spot-forming cells per 10^6 peripheral blood mononuclear cells.

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SPS: VZV Antibody (gpELISA) Titers by HZ Case Status

		ZOSTAVAX™ (N=691)		Placebo (N=704)	
	Case Status	n	Response (95% CI)	n	Response (95% CI)
Week 6 GMT	Developed HZ	9	271.9 (161.9, 456.7)	23	181.6 (133.5, 246.9)
	Did not develop HZ	658	478.4 (444.6, 514.7)	661	296.2 (273.3, 321.1)
Week 6 GMFR from Day 0	Developed HZ	9	1.1 (0.9, 1.4)	23	0.9 (0.8, 1.1)
	Did not develop HZ	646	1.7 (1.6, 1.8)	650	1.0 (1.0, 1.0)

GMFR = Geometric mean foldrise

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SPS: VZV IFN-γ ELISPOT Counts by HZ Case Status

		ZOSTAVAX™ (N=691)		Placebo (N=704)	
	Case Status	n	Response (95% CI)	n	Response (95% CI)
Week 6 GMC	Developed HZ	7	39.4 (7.9, 196.6)	21	17.4 (8.8, 34.4)
	Did not develop HZ	599	72.5 (63.9, 82.3)	621	32.2 (28.5, 36.4)
Week 6 GMFR from Day 0	Developed HZ	7	2.7 (0.6, 12.9)	21	1.1 (0.5, 2.2)
	Did not develop HZ	575	2.0 (1.8, 2.3)	590	0.9 (0.8, 1.1)

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SPS: VZV RCF by HZ Case Status

		ZOSTAVAX™ (N=691)		Placebo (N=704)	
	Case Status	n	Response (95% CI)	n	Response (95% CI)
Week 6 GMC	Developed HZ	9	7.0 (4.2, 11.6)	22	3.8 (2.4, 5.9)
	Did not develop HZ	659	9.7 (9.1, 10.5)	665	5.4 (5.0, 5.9)
Week 6 GMFR from Day 0	Developed HZ	9	3.1 (0.5, 19.2)	21	1.3 (0.8, 2.1)
	Did not develop HZ	633	1.7 (1.6, 1.8)	641	0.9 (0.8, 1.0)

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Criterion 3: Effect of Immune Responses on HZ Risk (Cox regression model)

- VZV Antibody and CMI Responses are inversely related to the risk of HZ
- But no “protective level” can be identified

One-log-unit Increase	HZ Risk Reduction (95% CI)	p-Value
gpELISA	38.0% (95% CI, 20.9%, 51.5%)	<0.001
ELISPOT	19.2% (95% CI, 4.6%, 31.5%)	0.017
RCF	26.4% (95% CI, 13.6%, 37.6%)	<0.001

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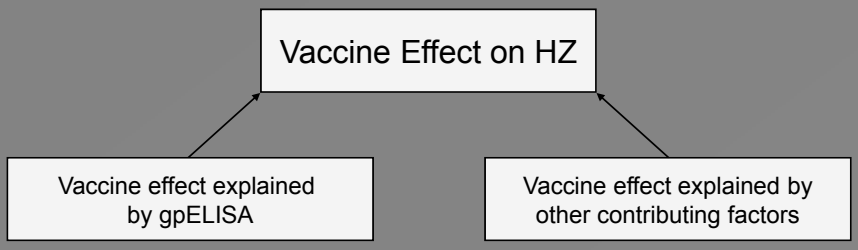
Proportion of VE_{HZ} Explained by Immune Responses at 6 Weeks Postvaccination

- Regression models can further break down the total vaccine effect on HZ into 2 components



log (Relative Risk due to vaccine effect) =
log (Relative Risk channeled through the immune marker)
+log (Relative Risk contributed by other factors, e.g. age)

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Proportion of VE_{HZ} Explained

- Moderate mediation of clinical efficacy by immune responses at week 6 and change from baseline

	Proportion of ZOSTAVAX™ Effect Explained by Immunogenicity Measurement
gpELISA	45.9% (95% CI, 13.0%, 100.0%)
IFN-γ ELISPOT	15.7% (95% CI, 3.0%, 90.4%)
RCF	24.4% (95% CI, 6.6%, 100.0%)

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Concerns About Proportion of Treatment Explained

- Imprecise, not well bounded by (0, 1)
- Highly variable with wide confidence interval

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Other Measures of Correlation

- Adjusted association
  - Buyse and Molenberghs 1998
  - Correlation between surrogate (S) and clinical outcome (T), adjusting for treatment effect (Z)
  - Bounded between (-1, 1)

$$\rho_Z = \mathrm{Corr}(S, T \mid Z)$$

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Other Measures of Correlation

- Adjusted likelihood reduction factor (LRF_{adj})
  - Alonso et al 2004
  - The LRF quantifies how much information is gained by adding surrogate (S) into a model with only treatment effect (Z) based on the likelihood ratio test (LRT)

$$LRF_{adj} = \frac{1 - \exp\{-\mathrm{LRT}(S + Z \mid Z)/n\}}{1 - \exp\{-\mathrm{LRT}(S + Z \mid 1)/n\}}$$

  - LRF_{adj} is bounded between (0, 1)
    - LRF_{adj} = 0 if surrogate and true endpoint are independent
    - LRF_{adj} = 1 if surrogate and true endpoint is perfectly correlated
  - General concept that can be applied in different settings

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Further Analysis of Correlations

Antibody titers by gpELISA	Proportion of Treatment Effect Explained (PTE)	LRF_{adj}
6-wk titers	0.293	0.550
Foldrise from baseline	0.286	0.363
Titer + foldrise	0.459	0.593
I[foldrise>1.52]	0.580	0.681
Titer + I[foldrise>1.52]	0.783	0.810

I[foldrise > 1.52] is a binary indicator of whether foldrise from baseline is > 1.52

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Summary of ZOSTAVAX Study 1

- Immune responses correlate with HZ risk
- Antibody responses (gpELISA) seems to have a better correlation than ELISPOT and RCF
- No threshold of immune responses can be identified as protective level (?)
- Antibody responses may be used in future studies to demonstrate responses to vaccine in bridging trials
  - gpELISA assay easier to run, more precise than ELISPOT and RCF
- A second efficacy study will also assess gpELISA antibody as a correlate of protection

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ZOSTAVAX Study 2 (Protocol 022): Efficacy Trial in 50-59 Year Olds

- N = 22,439 subjects 50-59 years of age randomized 1:1 to receive ZOSTAVAX® or placebo
- Case-cohort for immunogenicity measurement (Day 0 and Week 6)
  - A random sub-cohort (N=2,269)
  - All HZ cases (n=129)
  - VZV antibody responses by gpELISA
- Average of 1.3 years of HZ surveillance

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022 Immunogenicity Results

- ZOSTAVAX™ induced VZV-specific antibody responses gpELISA (units/mL) at 6 weeks postvaccination

	Geometric Mean Response (gpELISA)		
	Day 0	Week 6	Fold Rise
Vaccine (N=1136)	283.6	660.0	2.3 (95% CI: 2.2, 2.4)
Placebo (N=1133)	292.8	293.1	1.0 (95% CI: 1.0, 1.0)

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022: VZV Antibody (gpELISA) Titers by HZ Case Status

		ZOSTAVAX™ (N=1164)		Placebo (N=1223)	
	Case Status	n	Response (95% CI)	n	Response (95% CI)
Week 6 GMT	Developed HZ	24	454.1 (300.2, 687.0)	89	178.3 (140.0, 227.1)
	Did not develop HZ	1086	659.3 (624.1, 696.6)	1079	294.2 (275.7, 313.9)
Week 6 GMFR from Day 0	Developed HZ	24	1.6 (1.2, 1.9)	89	1.0 (0.9, 1.0)
	Did not develop HZ	1085	2.3 (2.2, 2.4)	1078	1.0 (1.0, 1.0)

GMFR = Geometric mean foldrise

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Correlate of Protection Analysis From Two Phase III Trials (Antibody Responses by gpELISA)

Study Protocol	Population	Vaccine Effect on incidence of HZ	Vaccine effect on antibody response	Correlation between antibody and risk of HZ
004 sub-study (n=1328)	60+ years	51% (p <.0001)	1.7 fold (p <.0001)	38% risk reduction per one-log-unit increase (p <.0001)
022 case-cohort (N=22439, n=2269)	50-59 years	70% (p <.0001)	2.3 fold (p <.0001)	31% risk reduction per one-log-unit increase (p <.0001)

VZV antibody response measures (natural log scale):
(1) gpELISA titer at 6 weeks
(2) gpELISA fold rise at 6 weeks (6-week titer/baseline titer)

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Proportion of Treatment Effect Explained (PTE) in 004 and 022

Antibody responses by gpELISA	004	022
6-wk titers	0.293	0.251
Foldrise from baseline	0.286	0.220
Titer + foldrise	0.459	0.426
Foldrise > Cutoff?	0.580	0.405
Titer + I[foldrise>cutoff]	0.783	0.645

Cutoff = 1.52 for protocol 004 and 1.44 for protocol 022

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Evaluating Principle Surrogate Using Causal Inference

ZOSTAVAX Example

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Evaluation of Principal Surrogate Endpoint Using Causal Inference Framework

- Concept of surrogate endpoint: "principal surrogate"
  - Frangakis and Rubin (2002)
  - Gilbert and Hudgens (2008)
- A biomarker is a principal surrogate if it satisfies:

  (1) Average causal necessity
  no impact on S → no impact on T

  (2) Average causal sufficiency
  impact on S → impact on T
- We validate principal surrogate based on single and multiple imputation procedures
- Show VZV antibody response satisfies both criteria to be a principal surrogate

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Notations and Potential Outcomes

T ~ Clinical Endpoint
S ~ Surrogate Endpoint
Z ~ Treatment

Each subject can be potentially assigned to BOTH control (Z=0) and treatment (Z=1) groups.

For every subject, there are TWO potential outcomes

$S_i(0)$ ~ potential surrogate resp. of subj. i if received control
$S_i(1)$ ~ potential surrogate resp. of subj. i if received treatment

$T_i(0)$ ~ potential clinical resp. of subj. i if received control
$T_i(1)$ ~ potential clinical resp. of subj. i if received treatment

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Notations and Potential Outcomes

		Observed Outcome in trials		Surrogate Outcome	
Treatment	Subject index	S	T	$S(0)$	$S(1)$
Z=0 (Control)	1	obs	obs	S_i^{obs}	
	2	obs	obs	S_i^{obs}	
	..	obs	obs	S_i^{obs}	
	m	obs	obs	S_i^{obs}	
Z=1 (Treatment)	m+1	obs	obs		S_i^{obs}
	m+2	obs	obs		S_i^{obs}
	..	obs	obs		S_i^{obs}
	n	obs	obs		S_i^{obs}

In control group, no potential outcome under treatment.
In treatment group, no potential outcome under control.

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Principal Stratification

Principal strata are defined by the pair of values of the potential outcomes $S(0)$ and $S(1)$, assuming both $S(0)$ and $S(1)$ are known. If S is a binary variable with levels Low and High, then based on the potential outcomes of $S(0)$ and $S(1)$, subjects can be classified into different strata:

If received placebo	If received vaccine	Note
$S_i(0) = Low$	$S_i(1) = High$	Vaccine has positive effect on S
$S_i(0) = Low$	$S_i(1) = Low$	Vaccine has no effect
$S_i(0) = High$	$S_i(1) = High$	Vaccine has no effect
$S_i(0) = High$	$S_i(1) = Low$	Vaccine has negative effect on S

The fourth stratum shows that the patient has high immunogenicity if received placebo and low immunogenicity if received vaccine, which should be empty theoretically.

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Definition of Principal Surrogate

Average causal necessity

$$\Pr[T(1) = 1 \mid S(0) = S(1) = s] = \Pr[T(0) = 1 \mid S(0) = S(1) = s]$$

Interpretation: Treatment cannot change the probability of HZ without changing S. ($S(0) = S(1) = s$ suggests treatment does not affect S.)

Average causal sufficiency

$\Pr[T(1) = 1 \mid S(0) = s_0, S(1) = s_1] \neq \Pr[T(0) = 1 \mid S(0) = s_0, S(1) = s_1]$ for all $| s_0 - s_1 | > c \geq 0$

Interpretation: $S(0) = s_0, S(1) = s_1 (s_0 \neq s_1)$ suggests that treatment has an impact on S. The inequality suggests that the treatment affects the clinical outcome T through the surrogate S. A change in S induces a change in probability of clinical outcome (T).

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Imputing 'Missing Values' of S(0) and S(1) (Miao, Li, Gilbert and Chan, 2013)

- Deterministic regression imputation (single imputation)

  The imputed values are exactly the predicted value based on the regression model and the predictive uncertainty is ignored. Only one set of the "complete" data is obtained after the imputation.

- Random regression imputation (multiple imputations)

  The imputed value for a particular patient is draw from a normal distribution with the predicted value of the patient as the mean and the prediction error as the standard deviation. Multiple imputations are carried out to account for the uncertainty in prediction.

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The "Complete" Dataset after Imputation

		HZ status	Potential Surrogate: 6-wk gpELISA titer	
Treatment Group	Patient	T	$S(0)$	$S(1)$
Z=0 (Placebo)	1	T_i^{obs}	S_i^{obs}	S_i^{imp}
	2	T_i^{obs}	S_i^{obs}	S_i^{imp}
	..	T_i^{obs}	S_i^{obs}	S_i^{imp}
	m	T_i^{obs}	S_i^{obs}	S_i^{imp}
Z=1 (Vaccine)	m+1	T_i^{obs}	S_i^{imp}	S_i^{obs}
	m+2	T_i^{obs}	S_i^{imp}	S_i^{obs}
	..	T_i^{obs}	S_i^{imp}	S_i^{obs}
	n	T_i^{obs}	S_i^{imp}	S_i^{obs}

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Imputation Model Selected for ZOSTAVAX

- Fit a linear regression model using data from the placebo group (Z=0) including baseline and 6-week antibody responses

  For those in the vaccine group, $S_i(0)$ is imputed based on this model.

- Fit a linear regression model using data from the vaccine group (Z=1) including baseline and 6-week antibody responses

  For those in the placebo group, $S_i(1)$ is imputed based on the above model.

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Evaluation of Principal Surrogate

- Categorize potential outcomes of immune responses (S) into 4 groups

S(0) or S(1)	Postvaccination Titer	Postvaccination Fold rise from baseline
1	Low	Low
2	High	Low
3	Low	High
4	High	High

- Define principal strata as 11, 22, …, 13, … according to pairs of S(0) and S(1)
- Evaluate average causal necessity and average causal sufficiency using imputation method

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Average Causal Necessity

(Results based on Single Imputation for illustration, P022)

Freq and Probability of HZ within the Principal Strata where Vaccine has no effect on the surrogate

		Stratum				
Frequency		11	22	33	44	Total
Placebo Group	HZ	0	13	0	3	16
	No HZ	0	204	1	103	308
	Pr(HZ=1) (%)	--	**5.99**	**0.00**	**2.83**	4.94
Vaccine Group	HZ	1	14	0	0	15
	No HZ	4	327	3	0	334
	Pr(HZ=1) (%)	**20.00**	**4.11**	**0.00**	--	4.30
Overall VE = 13% (p = 0.346)						

Causal necessity is satisfied: If vaccine does not change immunogenicity, then it does not change probability of HZ.

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Average Causal Sufficiency

(Results based on Single Imputation for illustration, P022)

Freq and Probability of HZ within the stratum where vaccine had an effect on surrogate

		Stratum					
Frequency		12	13	14	24	34	Total
Placebo Group	HZ	0	1	35	35	1	72
	No HZ	0	5	156	582	17	760
	Pr(HZ=1)	--	**16.67**	**18.32**	**5.67**	**5.56**	8.65
Vaccine Group	HZ	0	2	0	7	0	9
	No HZ	3	21	158	568	0	750
	Pr(HZ=1)	**0.00**	**8.70**	**0.00**	**1.22**	--	1.19
Overall VE = 86.3% (95% CI: 72.5%, 94.0%), p<0.001							

Causal sufficiency is satisfied: When there is a change in immunogenicity ($S(0) \neq S(1)$), there is also a change in the probability of HZ.

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Multiple Imputations

The imputation was repeated multiple times based on regression models to obtain 1000 "complete" datasets. For each imputed dataset, estimate the treatment effect within the principal strata based on Cox regression model with age and gender as the covariates:

- the total number of observations in each stratum
- the p-value of the treatment effect from the Cox regression model
- the estimated treatment effect (hazard ratio) from the Cox regression model

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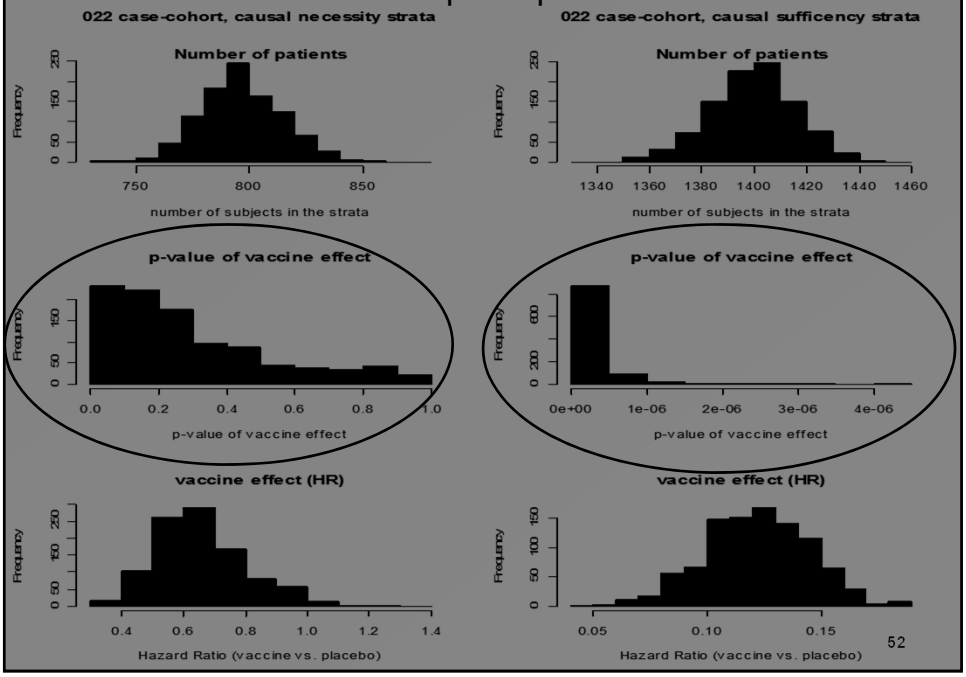
Results from Multiple Imputations – P022



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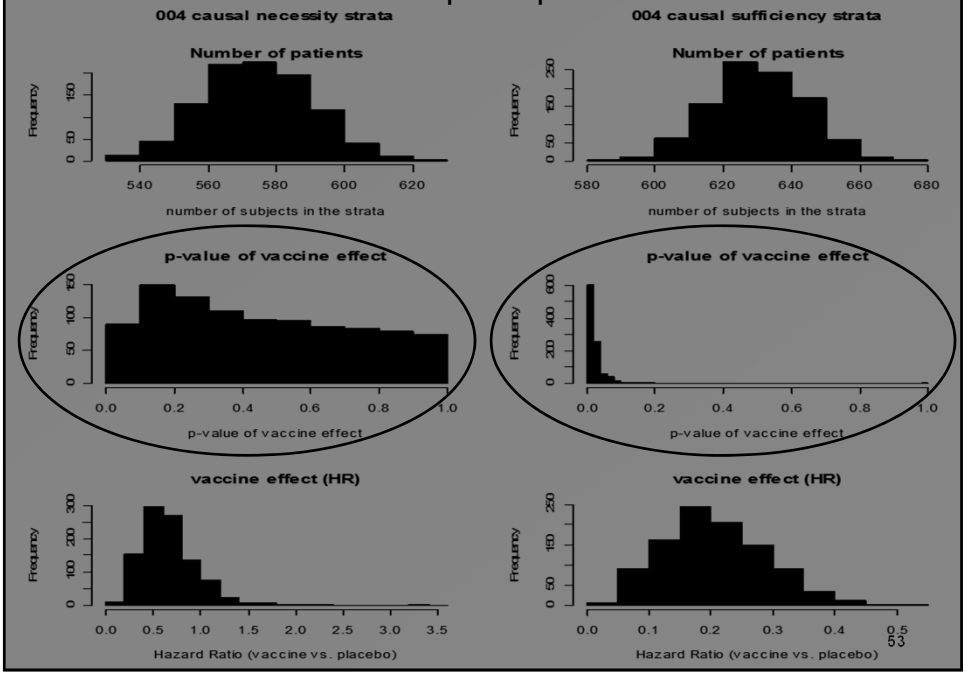
Results from Multiple Imputations – P004



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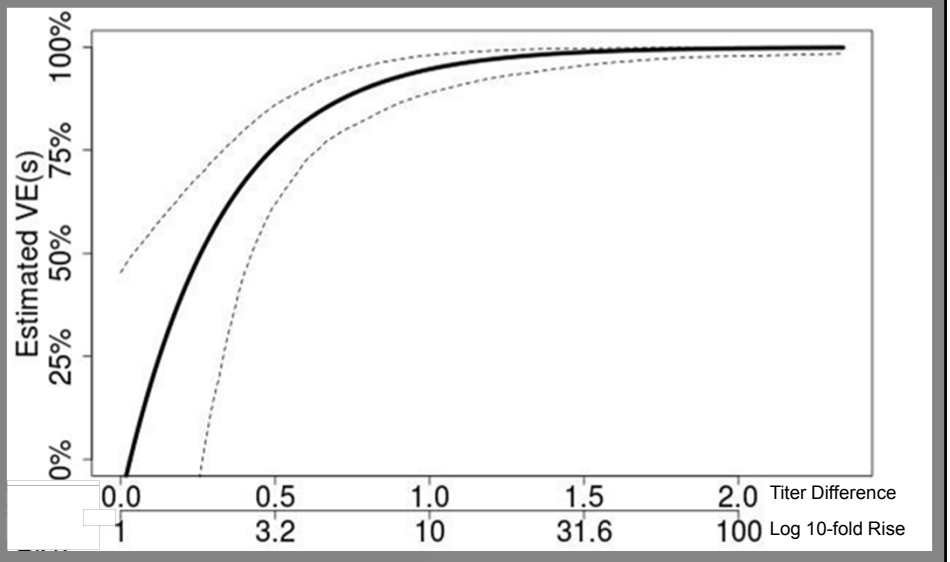
Vaccine Efficacy Curve



Gabriel, Gilbert and Chan et al. ongoing research

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Summary of ZOSTAVAX® Example

- VZV antibody response is shown to be predictive of vaccine efficacy based on
  - Prentice's criteria
  - Principal surrogacy of the causal inference framework
- Results are consistent across two trials with different age populations

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Further Comments

- Some scientists believe cell-mediated immunity (CMI) is the major causal agent for protection of herpes zoster
- But VZV antibody response is easier to measure with greater reliability than CMI responses
  - Established as a non-mechanistic correlate of protection
- VZV antibody response is accepted as a primary endpoint in subsequent ZOSTAVAX® trials to evaluate
  - Formulation changes
  - Concomitant use with other vaccines

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Design Considerations For Evaluating Correlates of Protection

Subsampling Methods

(Zhao, Wang, Chan, FDA/Industry Workshop 2008)

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Design Considerations

- Need to collect immunogenicity data in an efficacy trial
- Due to logistic and resource constraints, often difficult or even infeasible to collect blood samples from the whole cohort
  - e.g., hard to ship and measure CMI for all 38,000 subjects in a vaccine efficacy trial
- Flexible subsampling methods needed

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Flexible Subsampling Methods

- Nested case-control method
- Case-cohort method
- "Hybrid" method
- Common features
  - Subsample = all cases + some non-cases
  - Feasible when the covariate history is potentially accessible for each cohort member
  - Sampling done for full cohort and stored in the site for future shipping and analysis
  - Cox proportional hazards model is the base

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The Nested Case-Control Method

- Conduct case-control study nested in the full cohort
- Cases and controls are matched by potential confounding covariates
  - Matching ratio is 1:m ($m \leq 6$ in general)
- Controls are from same population as cases

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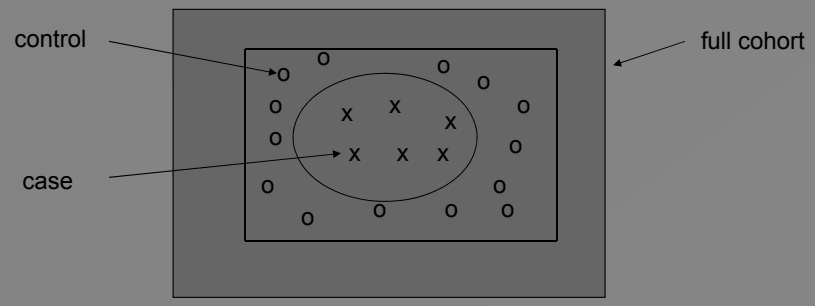
The Nested Case-Control Method



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Potential Issues with the Nested Case-Control Method

- Finding the right matches is not simple
- Usually the selected matches may not be strictly representative
- Not good if the confounding factors are not clear

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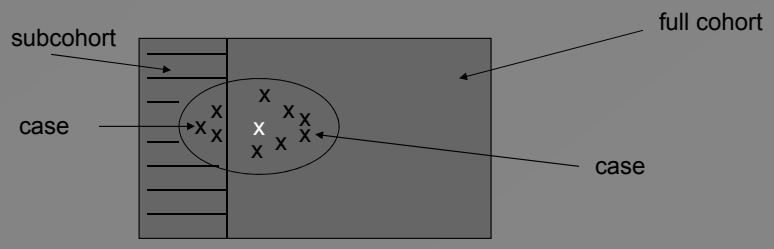
The Case-Cohort Method

- A subcohort randomly selected from the full cohort
- Analysis population = cases + subcohort



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The Case-Cohort Method

- Prospective follow-up studies
- Allow assessment of relationship between exposure and outcomes other than the outcome of interest in the cohort sample, since the control group is a sample of the total reference population
  - Multiple endpoints of interest
- Observational epidemiologic studies for vaccine effectiveness – logistic model for vaccination status on cases, community acquired diseases (vaccination coverage)

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Parameter Estimates from The Case-Cohort Method

- Regression parameter estimate is consistent (Prentice 1986)
- "Standard" variance estimator based on partial likelihood
  - The inverse of the information matrix underestimates the variance
- Asymptotic variance estimator (Self & Prentice 1988)
  - Simplified by decomposing into two parts (Therneau & Li 1999; Langholz &Jiao 2007)
  - Can be implemented by using Cox regression software returning *dfbeta* residuals, e.g., SAS PHREG or Splus coxph

$$V = I^{-1} + (1 - n_{sc} / n_c) D'_{sc} D_{sc}$$

- Jackknife robust variance estimator (Barlow 1994)
  - Empirical version of the asymptotic variance
  - Can be used in more complex sampling schemes

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The Hybrid Method

- Combine the case-cohort and the case-control concept
- A subcohort is randomly sampled
- For cases outside the subcohort, matched controls are selected from outside subcohort
- case-cohort analysis within subcohort
- case-control analysis outside subcohort

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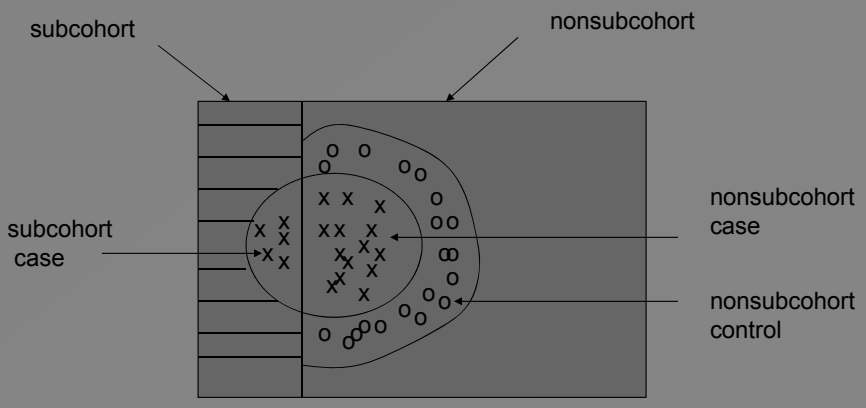
The Hybrid Method



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Simulation Settings for Comparison of subsampling methods

- Vaccine time-to-event efficacy trial with 1:1 randomization ratio in vaccine and placebo group, drop out rate 5% across; maximum follow-up 2 years; vaccine efficacy 64%; true biomarker effect $\beta_0 = 0.5$
  - Vaccine group: $\log(gpELISA) \sim N(6.2, 1.21)$
  - Placebo group: $\log(gpELISA) \sim N(5.7, 1.21)$
- Survival time S_i for the ith subject

$$S_i = -\frac{\log U_i}{\lambda_j \exp\{\beta_0 Z_i\}}$$

where $U_i \sim$ i.i.d. $U(0, 1)$, Z_i = log(gpELISA), j = vaccine, placebo

- Case-control matching: 1:5 ratio by age and treatment group

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Comparison of Subsampling Methods: Simulation I

N = 20300, average case number = 113, subcohort proportion = 10%

Average N in analysis	Beta_hat	Sample Variance	Standard Variance	Asymptotic Variance	Jackknife Robust Variance
Full Cohort 20300*	0.5000	0.0075	0.0074 **0.0149****		
Case Cohort 2132	0.5011	0.0083	0.0074 **0.0158**	0.00820 **0.01653**	0.00816 **0.01649**
Case Control 678	0.5071	0.0104	0.0101 **0.0205**		
Hybrid 2640	0.5035	0.0098	0.0097 **0.0195**		

**: numbers in bold type denote mean square errors

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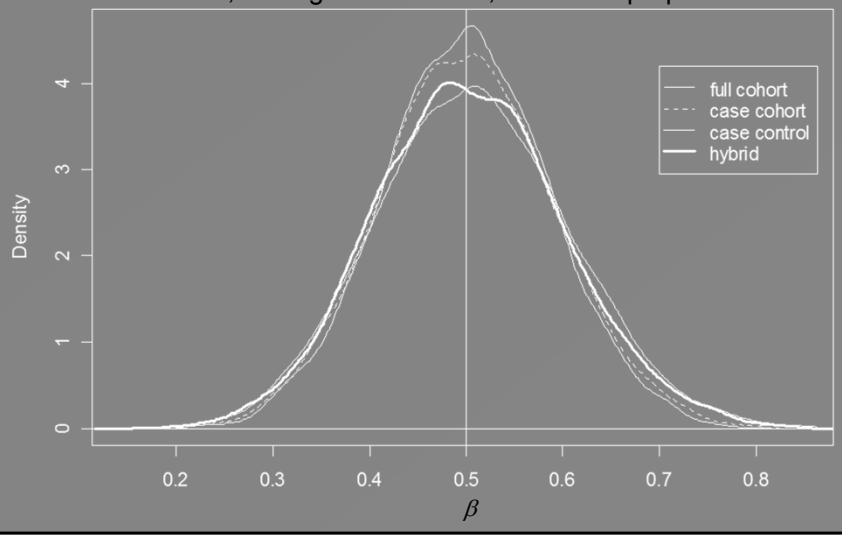
Kernel Density of Regression Parameter Estimate: Simulation I

N = 20300, average cases = 113, subcohort proportion = 10%



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Comparison of Subsampling Methods: Simulation II

N = 20300, average cases = 113, subcohort proportion = 2.8%

	Beta_hat	Sample Variance	Standard Variance	Asymptotic Variance	Jackknife Robust Variance
Full Cohort 20300	0.4993	0.0074	0.0074 **0.0148**		
Case Cohort 678	0.5041	0.0108	0.0075 **0.0184**	0.01046 **0.02130**	0.01049 **0.02133**
Case Control 678	0.5048	0.0101	0.0100 **0.0202**		
Hybrid 1227	0.5053	0.0100	0.0099 **0.0200**		

Note: This simulation is designed so that #pts for analysis are equal for case -cohort and case-control method

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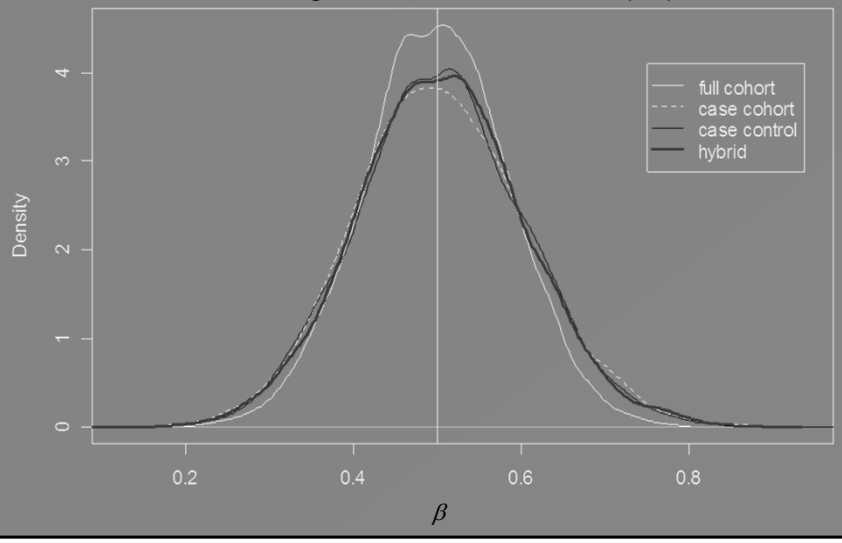
Kernel Density of Regression Parameter Estimate: simulation II

N = 20300, average cases = 113, subcohort proportion = 2.8%



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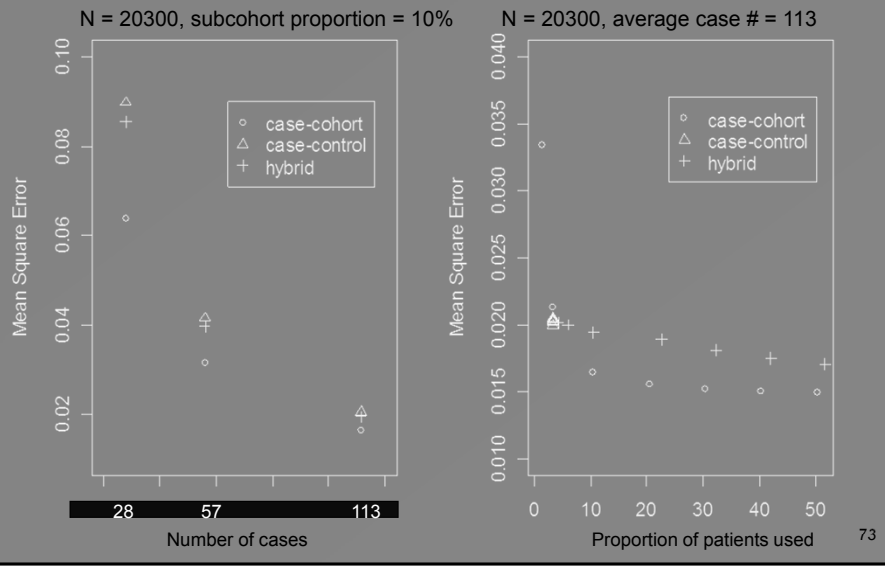
Comparison of subsampling methods performances: simulation



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Subsampling Design Summary

- Subsampling methods are efficient for large scale vaccine studies, both statistically and logistically
- Generally, case cohort design can be recommended
  - Relatively easy to operate
  - Stable performance and solid theoretical derivation
  - Reduction of sample size is often much greater than the reduction of relative efficiency, with respect to the full cohort
- Should be careful in using subsampling methods when N or # of cases is small (considerable bias)

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Power Calculation for The Case-Cohort Method

- For continuous covariate (Cai, Zeng 2007, based on pseudo-score statistic in Wacholder, Gail and Pee, 1991)

$$\Phi\left(Z_\alpha + (nq)^{1/2}\theta\sqrt{\frac{\sigma_x^2 p_D}{q+(1-q)p_D}} \right)$$

- For binary covariate (Cai, Zeng 2004)

$$\Phi\left(Z_\alpha + (nq)^{1/2}\theta\sqrt{\frac{p_1 p_2 p_D}{q+(1-q)p_D}} \right)$$

n: total number of subjects in full cohort
q: sampling proportion of the subcohort
θ: log-hazard ratio
σ^2_x: variance of covariate
P_D: observed failure rate after censoring
p_1, p_2: proportion of the two groups of the binary covariate

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