

Augmented designs to assess immune response in vaccine trials

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VAX004

- First Phase III trial of an HIV vaccine
- 5403 people participated
- Measured antibody response to vaccine two weeks after vaccination in *vaccine* group.
- Looked at risk of infection as a function of antibody response.

VAX004: Relative Risk of Infection Within Vaccine Group

GROUP	IMMUNE RESPONSE QUARTILE				
	Weak	Modest	Good	Best	
Vaccine	1.00	.43*	.34*	.29*	

* p<.05

VAX004: Relative Risk of Infection Both Groups

IMMUNE RESPONSE QUARTILE

GROUP	Weak	Modest	Good	Best	
Placebo	?	?	?	?	1.00
Vaccine	1.67*	.98	.87	.74	

* p<.05

What does this mean?

- Association: The vaccine is useless, but those individuals who could mount a strong immune response are better able to remain uninfected.
- Causation: The vaccine tends to cause infections in those who have poor immune response, but may prevent infections in those with good immune responses.

Suppose

- Phase III study with infection rates
10% placebo, 8% vaccine group
Risk gradient seen like VAX004.
- After celebration over, tinker with vaccine
to boost specific immune responses
- Could this be a waste of time?

Goal

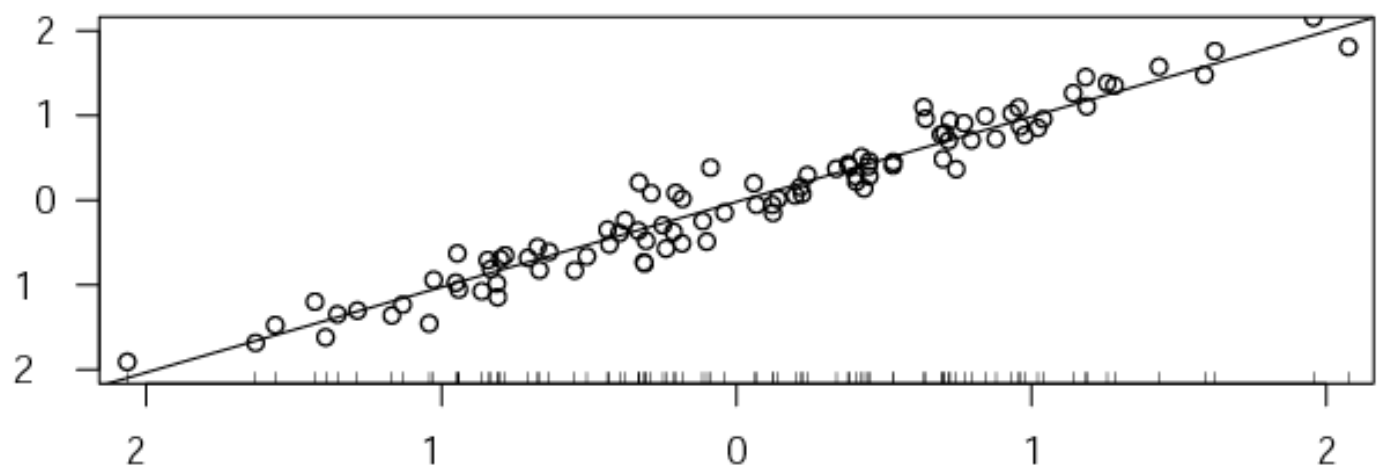
- Replace the ?s with numbers. Want to know if immune response is associated or causative
- We'll discuss two different and complementary approaches
 - Baseline Irrelevant Vaccination (BIV)
 - Closeout Placebo Vaccination (CPV)
- These can be used together or separately.

Baseline Irrelevant Vaccination (BIV)

- At baseline, measure something(s) correlated with X e.g. inoculate everyone with rabies vaccine.
- Shortly afterwards, measure immune response to rabies vaccine, say W .
- Randomization ensures (X, W) same in both groups.
- Use a placebo patient's W to impute X .

Vaccine Group

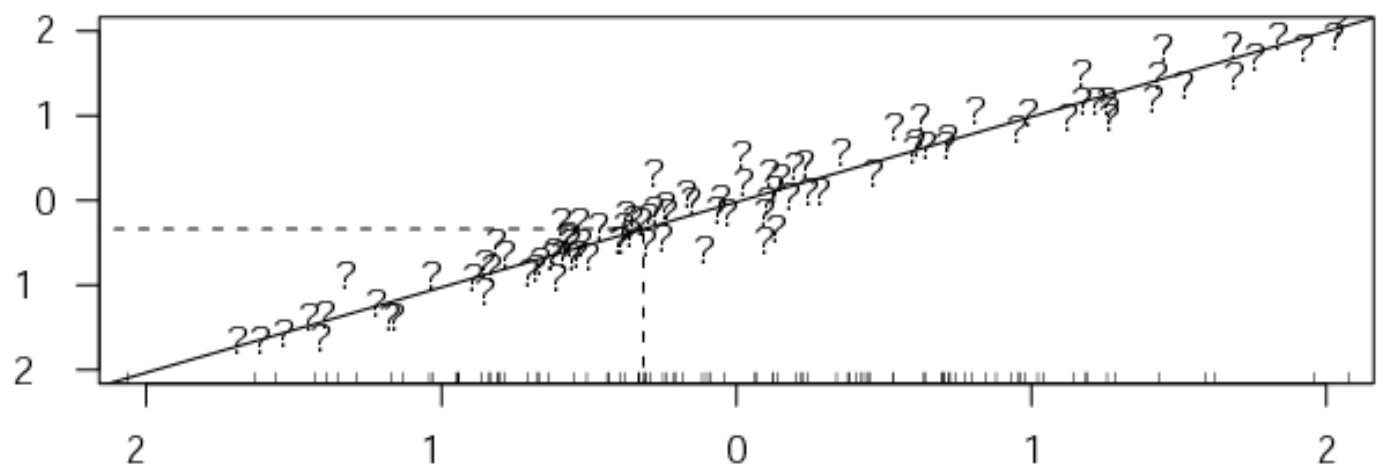
Immune response to HIV Vaccine



Immune response to Rabies Vaccine

Placebo Group

Immune response to HIV Vaccine



Immune response to Rabies Vaccine

Closeout Placebo Vaccination

- At the end of the trial, inoculate placebo uninfecteds with HIV vaccine.
- Shortly after inoculation, measure immune response X_C .
- Pretend X_C is what we would have seen, had we inoculated at baseline ie $= X_0$.

Usual Trial

Immune Response Quartiles

Group	Outcome	Weak	Modest	Good	Best	Total
Vaccine	Uninfected	70	85	90	95	340
	Infected	30	15	10	5	60
	Total	100	100	100	100	400
Placebo	Uninfected	?	?	?	?	340
	Infected	?	?	?	?	60
	Total	?	?	?	?	400

Usual Trial Exploiting Randomization

Immune Response Quartiles

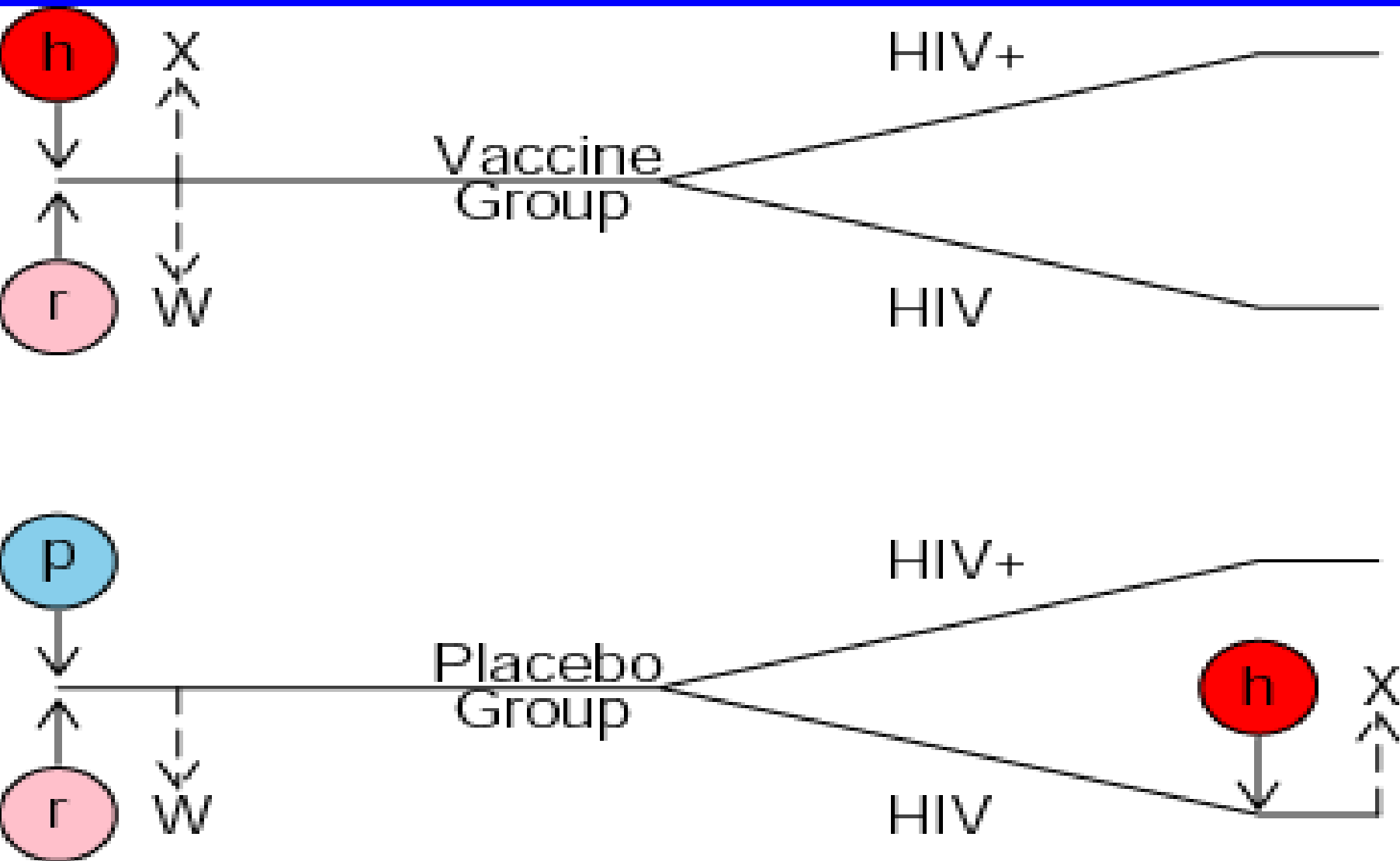
Group	Outcome	Weak	Modest	Good	Best	Total
Vaccine	Uninfected	70	85	90	95	340
	Infected	30	15	10	5	60
	Total	100	100	100	100	400
Placebo	Uninfected	?	?	?	?	340
	Infected	?	?	?	?	60
	Total	~100	~100	~100	~100	400

Trial with CPV (association)

Immune Response Quartiles

Group	Outcome	Weak	Modest	Good	Best	Total
Vaccine	Uninfected	70	85	90	95	340
	Infected	30	15	10	5	60
	Total	100	100	100	100	400
Placebo	Uninfected	71	84	92	93	340
	Infected	~29	~16	~8	~7	60
	Total	~100	~100	~100	~100	400

Schematic of BIV & CPV



Assumptions

- No noncompliance
- No missing data
- Infections start after X_0 is measured
- X_{0i} can be viewed as a baseline covariate
- Time constancy of immune response:

$$X_{Ci} = X_{0i}$$

What is X?

- X is the *potential* HIV specific immune response to HIV vaccination
- Vaccine: What a patient *did* produce in response to the vaccine. (*realized*)
- Placebo: What a patient *would* produce in response to the vaccine. (*unrealized*)

Probit Regression

- Assume the probability of infection varies smoothly with X .
 - Placebo Group:

$$P(Y = 1 | X) = \Phi(\beta_0 + \beta_2 X)$$

- Vaccine Group:

$$P(Y = 1 | X) = \Phi(\beta_0 + \beta_1 + (\beta_2 + \beta_3) X)$$

Maximum likelihood estimation

- We need X for $P(Y=1 | X, Z)$
 - Vaccine group, use X_0
 - Placebo Uninfected use X_C
 - Placebo Infecteds: Integrate $P(Y=1 | X, 0)$ with respect to the distribution of $X|W$

$$p^*(w) = E[\Phi(\beta_0 + \beta_2 X)] = \Phi\left(\frac{\beta_0 + \beta_2 \mu(w)}{\sqrt{1 + (\beta_2 \sigma^*)^2}}\right)$$

Likelihood

- Vaccine contribution

$$\prod_{i \text{ in } V} p_v(\mathbf{x}_{0i})^{y(i)} (1 - p_v(\mathbf{x}_{0i}))^{1 - y(i)}$$

- Placebo contribution

$$\prod_{i \text{ in } P(U)} (1 - p_p(\mathbf{x}_{Ci}))^{1 - y(i)} \prod_{i \text{ in } P(I)} p^*(\mathbf{w}_i)^{y(i)}$$

- \mathbf{x}_{0i} \mathbf{w}_i at baseline, \mathbf{x}_{Ci} at closeout

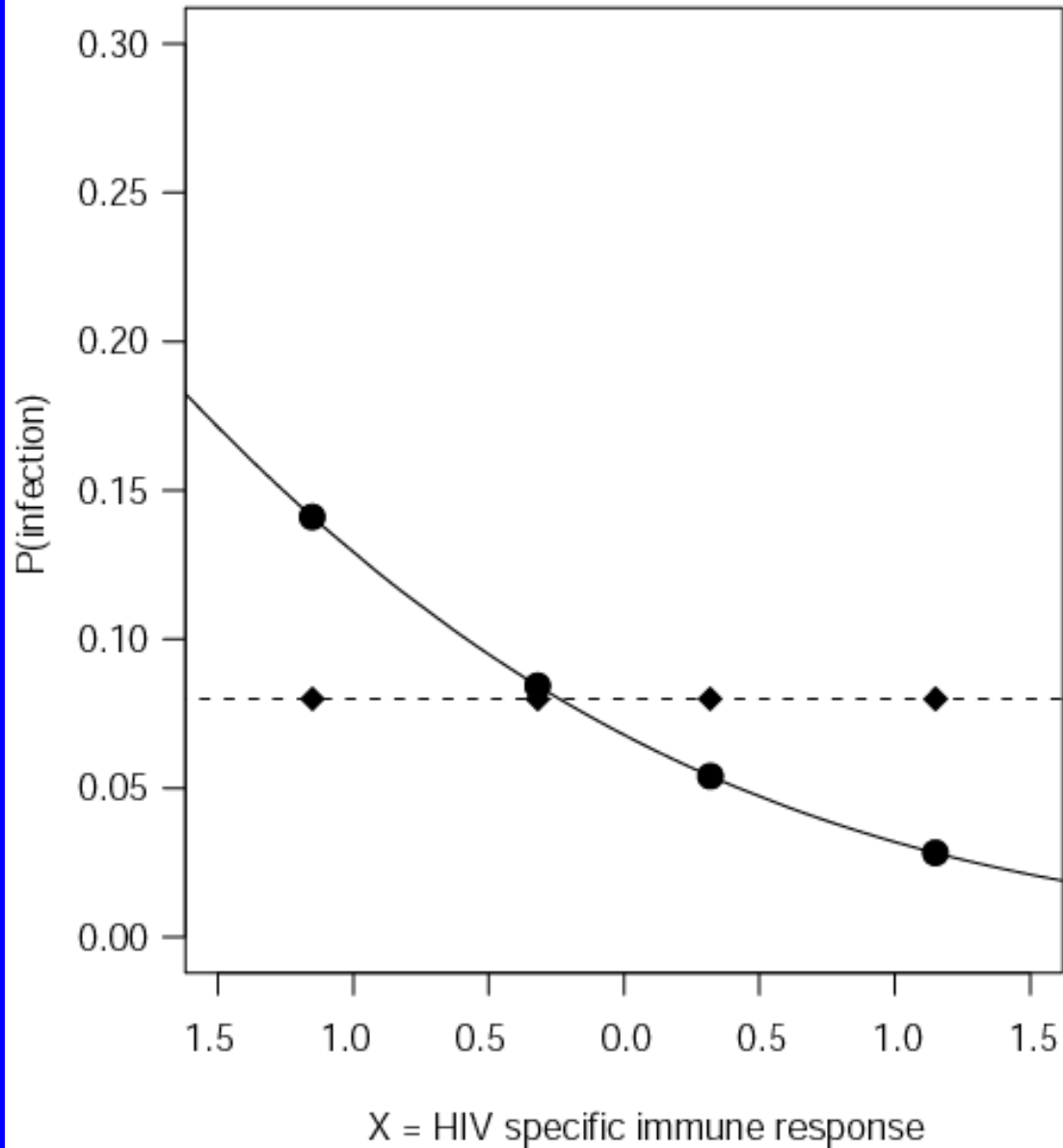
Maximum Likelihood

- Likelihood maximized using R
- Bootstrap used to estimate standard errors of parameters for Wald Tests.

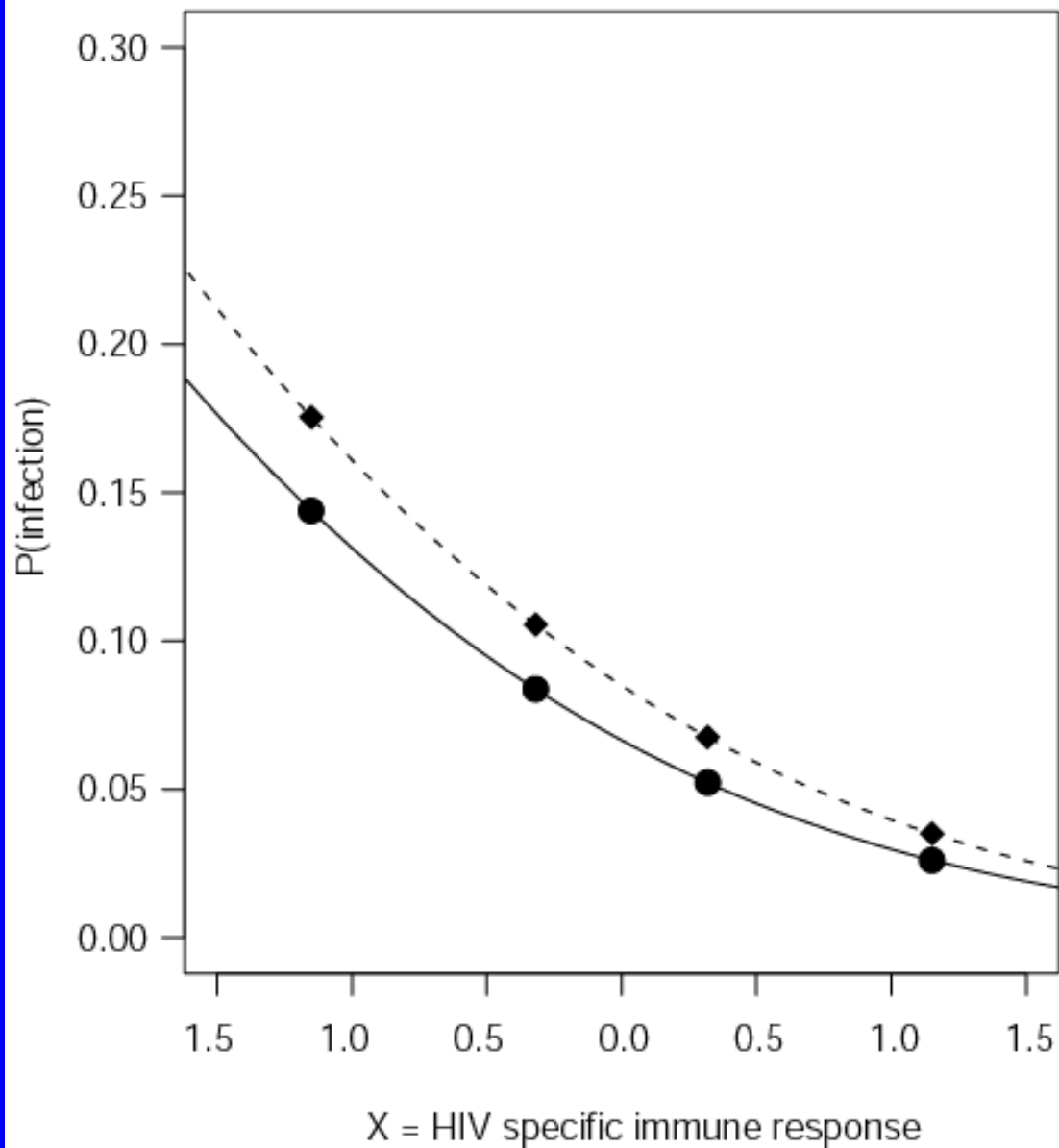
Simulation

- $N=1000$ per group
- Infection rates P, V 10%, 8%
- Causation
 - Gradient in Vaccine group, none in placebo
- Association
 - Similar gradient in both groups.
- X, W correlation 0, .25, .50, .75, 1

Causation: P(infection) by model and in quartiles



Association: P(infection) by model and in quartiles



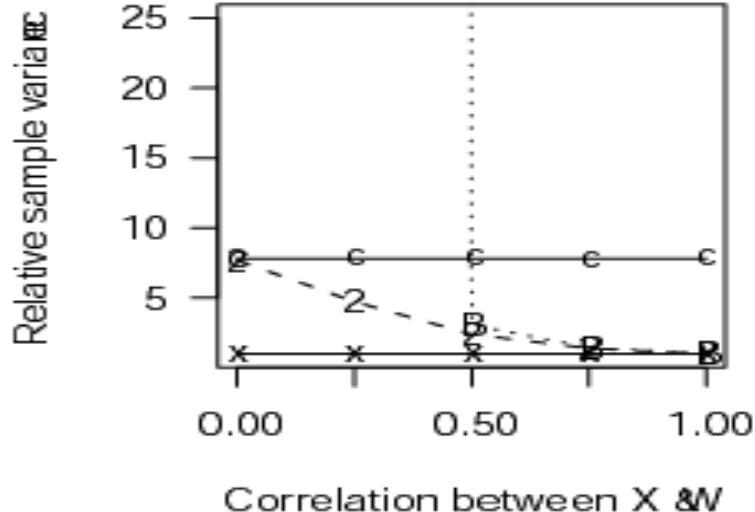
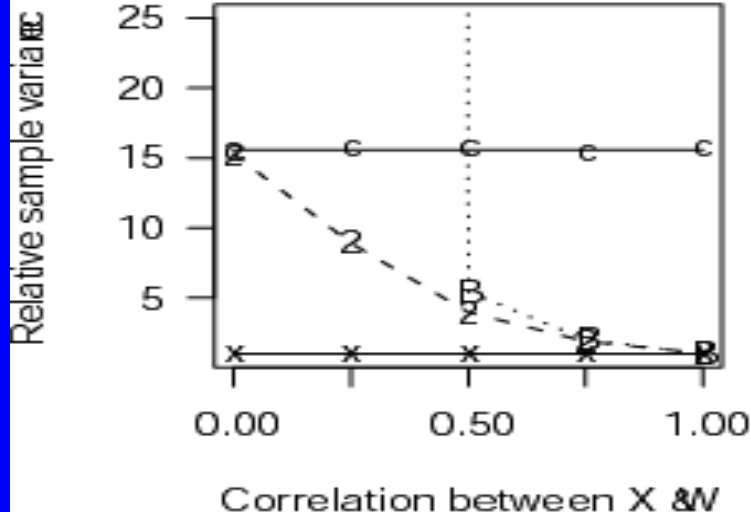
Results

- Measure performance by sample variance.
- Association Scenario $\rho = .5$

Design	Variance of β_2 estimate	Relative Variance
CPV	.0575	15.5
BIV	.0199	5.4
CPB+BIV	.0145	3.9
X known	.0037	1.0

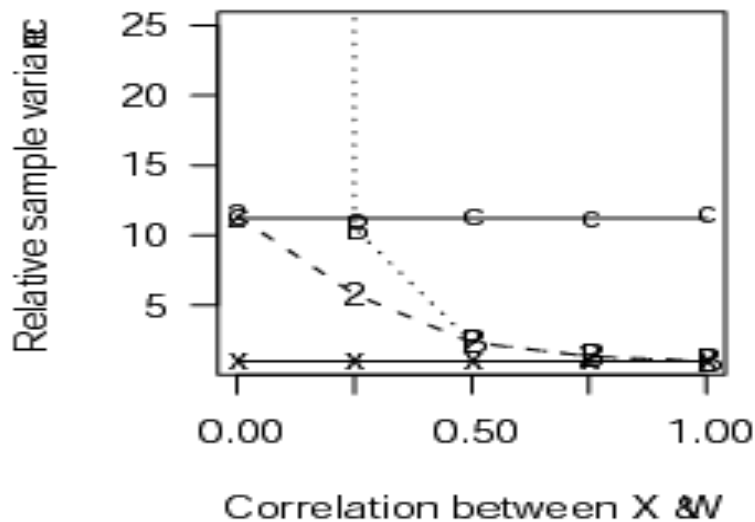
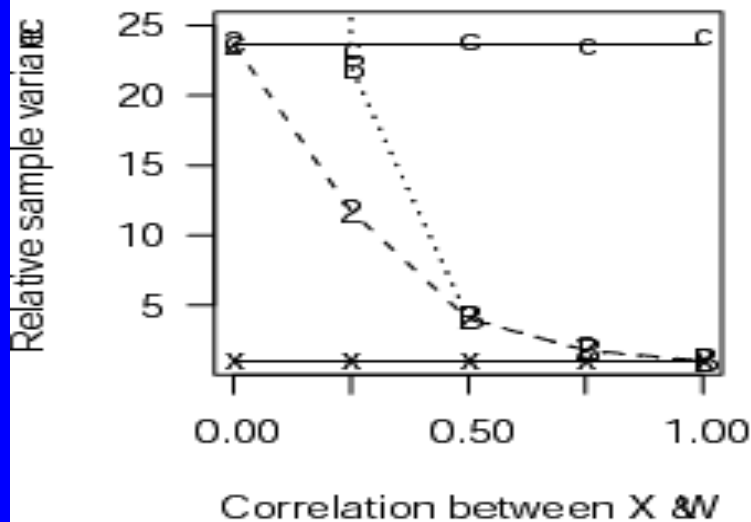
Association scenario beta_2

Association scenario beta_3



Causation scenario beta_2

Causation scenario beta_3



Performance depends on ρ

- If $\rho > .50$, little need for CPV
- If $\rho = .25$, both CPV and BIV are helpful.
- If $\rho = 0$, BIV useless.
- If $\rho = 1$, CPV useless.

Statistical Power BIV alone

- $\rho = .5$ N=2000/5000 180/450 infections

β_2	β_3	Scenario
.86/1.00	.03/.05	Association
.04/.05	.78/.99	Causation
.57/.95	.35/.65	Both

Is an improved vaccine good enough?

- Suppose Vaccine A had 20% VE
- Small studies of A* showed the immune response is increased by Δ .
- Will this be enough to launch a new trial?
- Using our statistical model, we can estimate the VE for A*, say VE^* . Is it worth spending \$100M?

Go/No go decision based on VE^* , not Δ .

Summary

- BIV and CPV can be added onto standard vaccine trials to replace the “?”s in the placebo group.
- Vaccine development focuses on cultivating the best immune response. But
 - immune response may be partly causative
 - different responses may be more/less causative
- Important to consider augmented designs to properly assess role of immune response
- Could incorporate BIV in phase 1 or 2 trials to assess correlation.

Thanks

- Peter Gilbert
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- Cliff Lane
- Ed Tramont