Augmented designs to assess immune response in vaccine trials

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NIAID

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

	IMMUNE RESPONSE QUARTILE				
GROUP	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

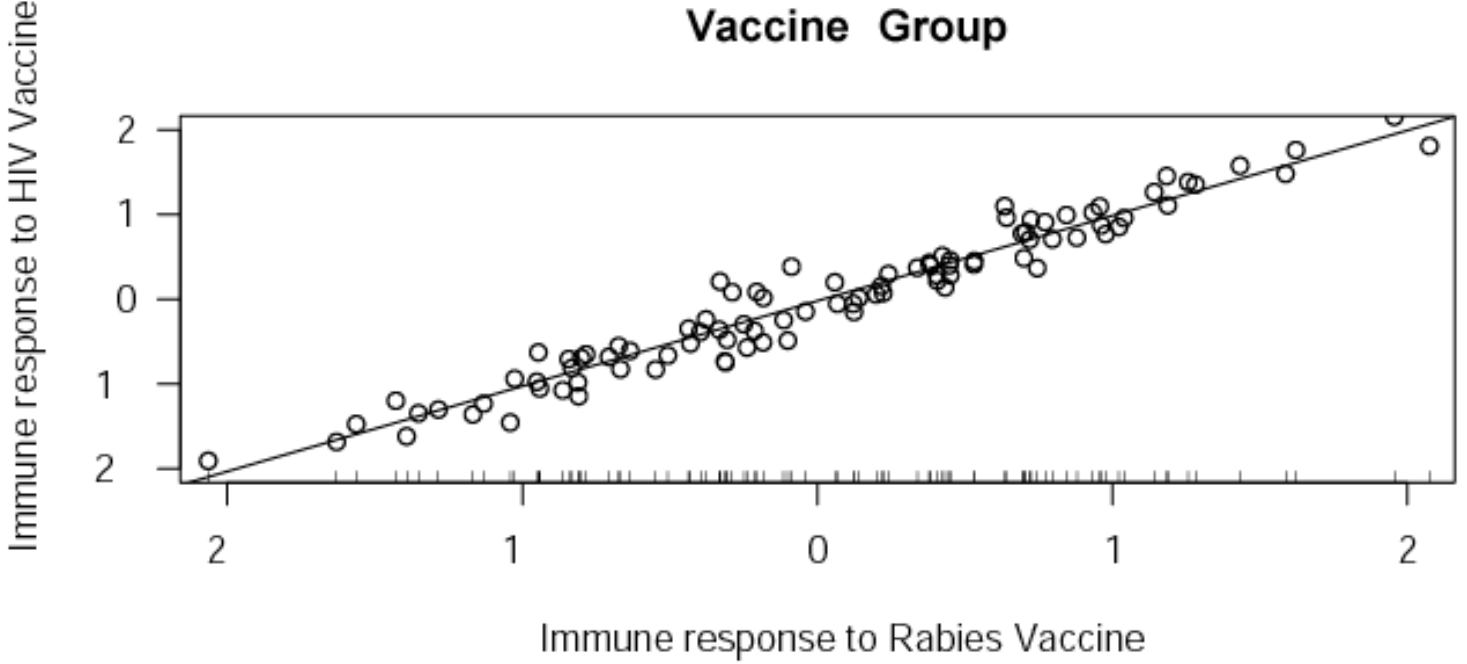
- Phase III study with infection rates
  10% placebo, 8% vaccine group
  Risk gradient seen like VAX004.
- After celebration over, tinker with vaccine to boost specific immune responses
- Could this be a waste of time?

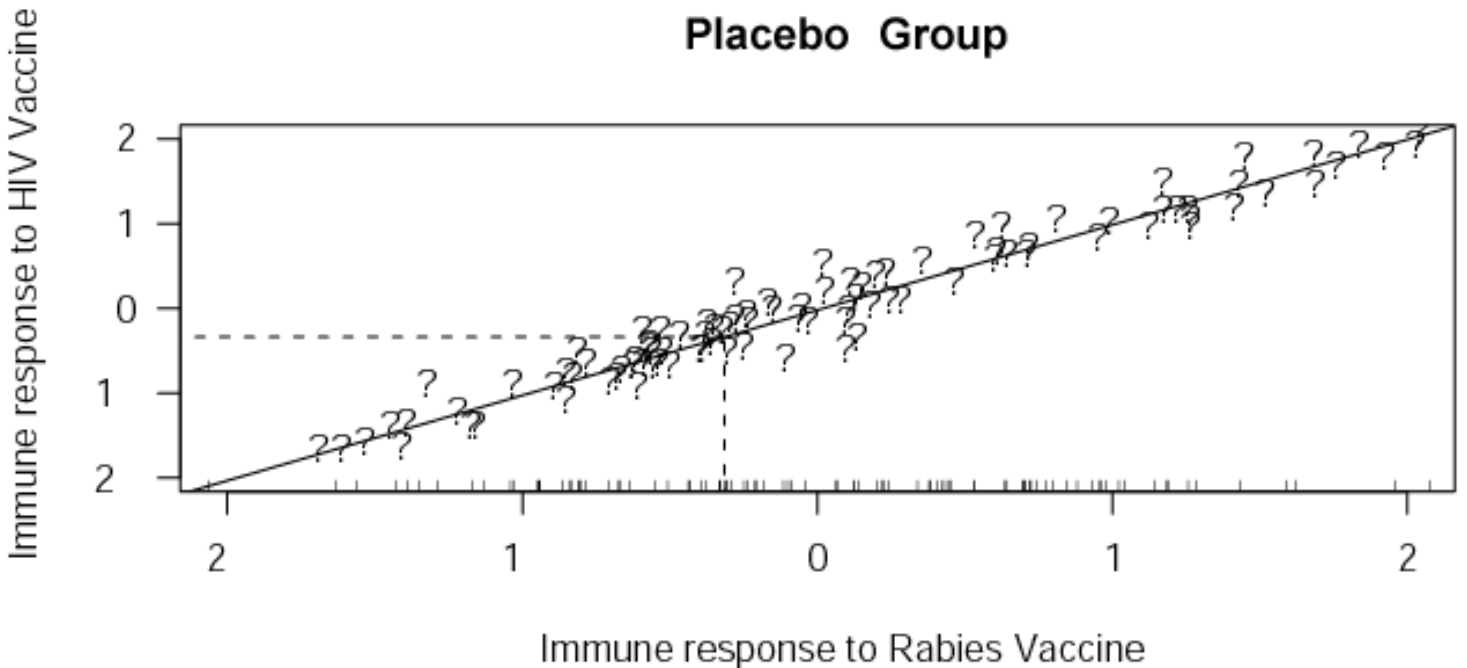
Goal

- 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
2
1
0
1
2
2
1
0
1
2
Immune response to Rabies Vaccine


Placebo Group
Immune response to HIV Vaccine
2
1
0
1
2
2
1
0
1
2
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**

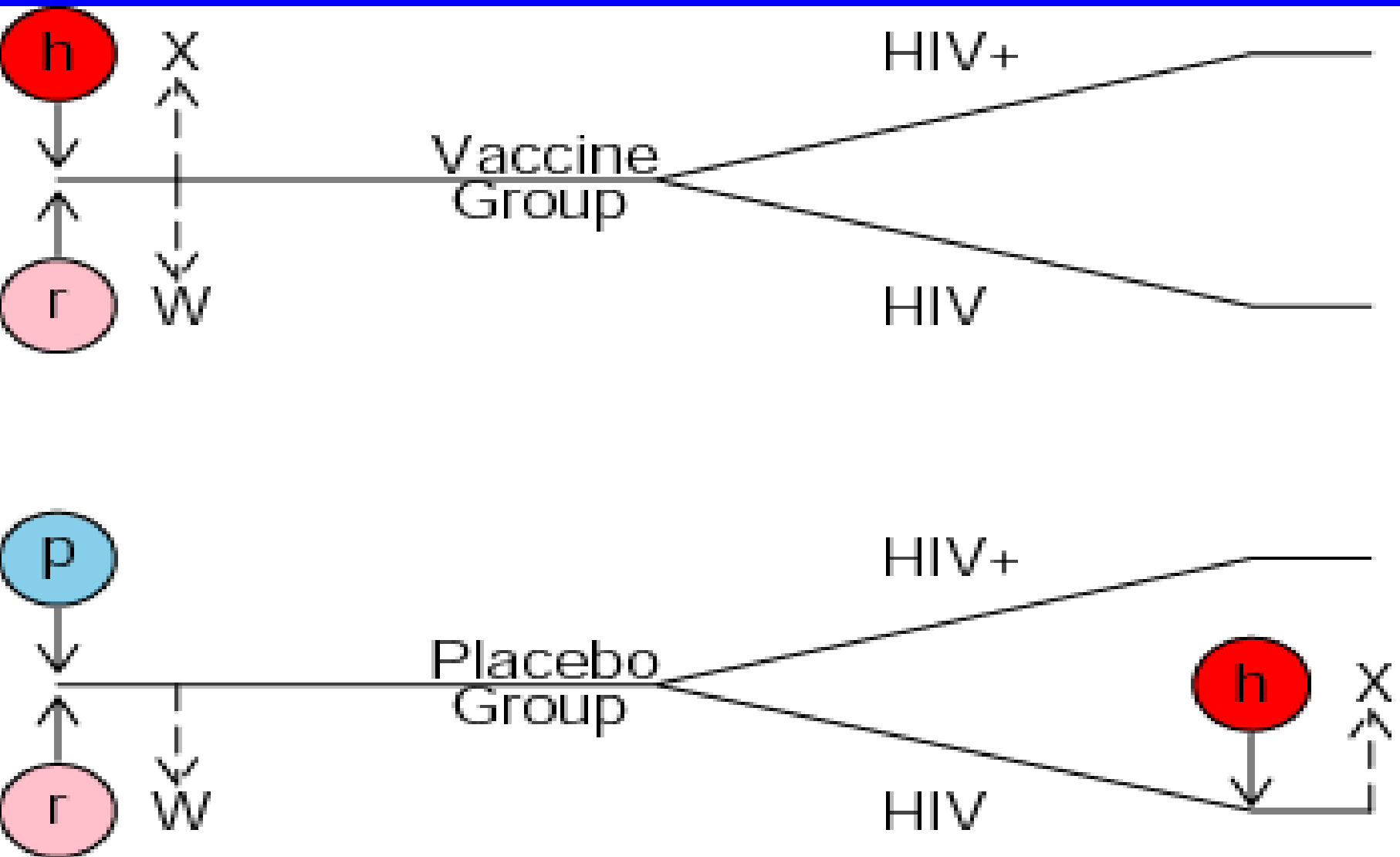
Usual Trial Exploiting Randomization

		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

$$\Pi_{i \text{ in } V} \; p_v(x_{0i})^{\,y(i)} \; (1 - p_v(x_{0i}))^{\,1 - y(i)}$$

- Placebo contribution

$$\Pi_{i \text{ in } P(U)} (1 - p_p(x_{Ci}))^{\,1 - y(i)} \; \Pi_{i \text{ in } P(I)} p^*(w_i)^{\,y(i)}$$

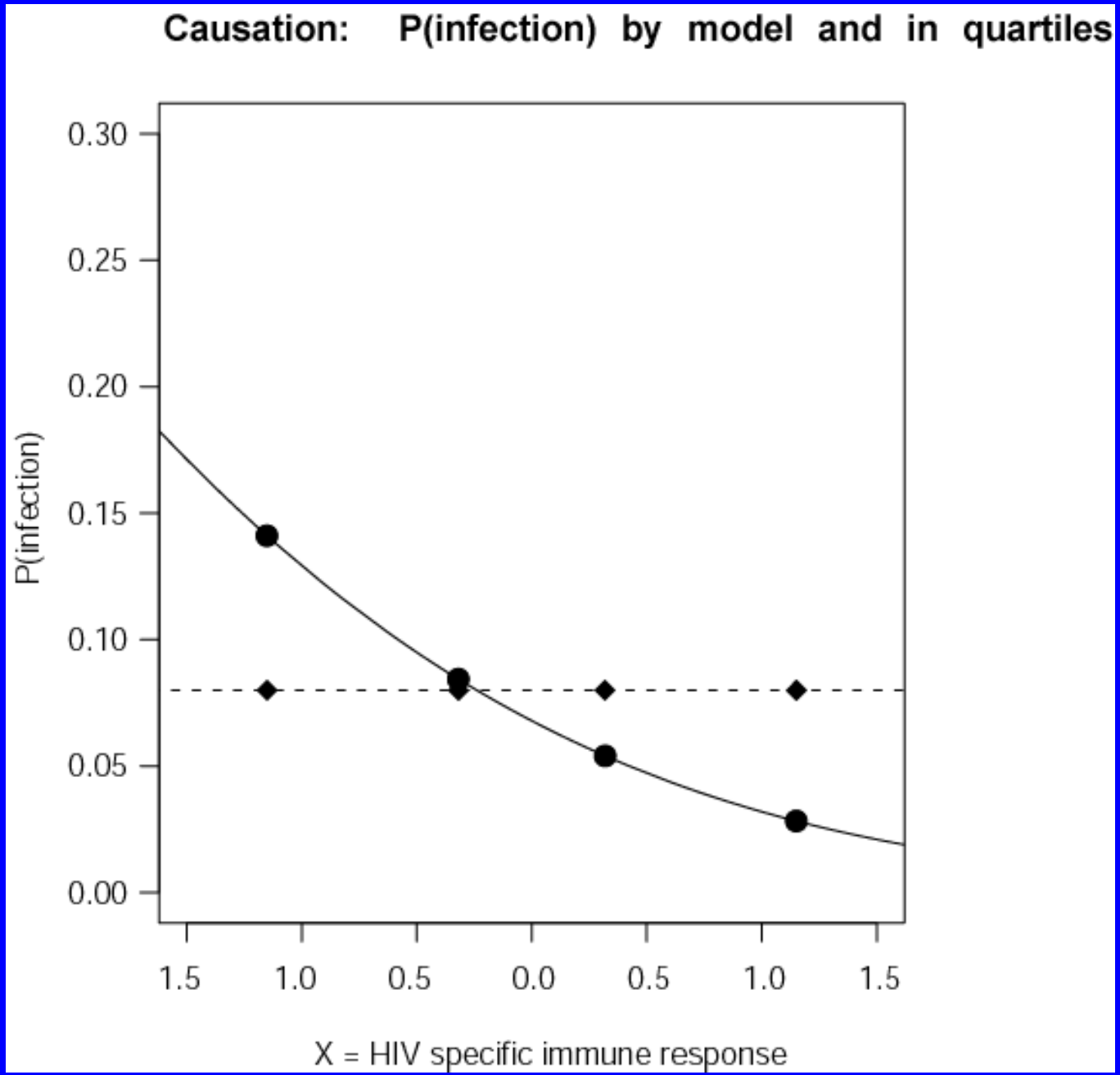
- x_{0i} w_i at baseline, x_{Ci} at closeout

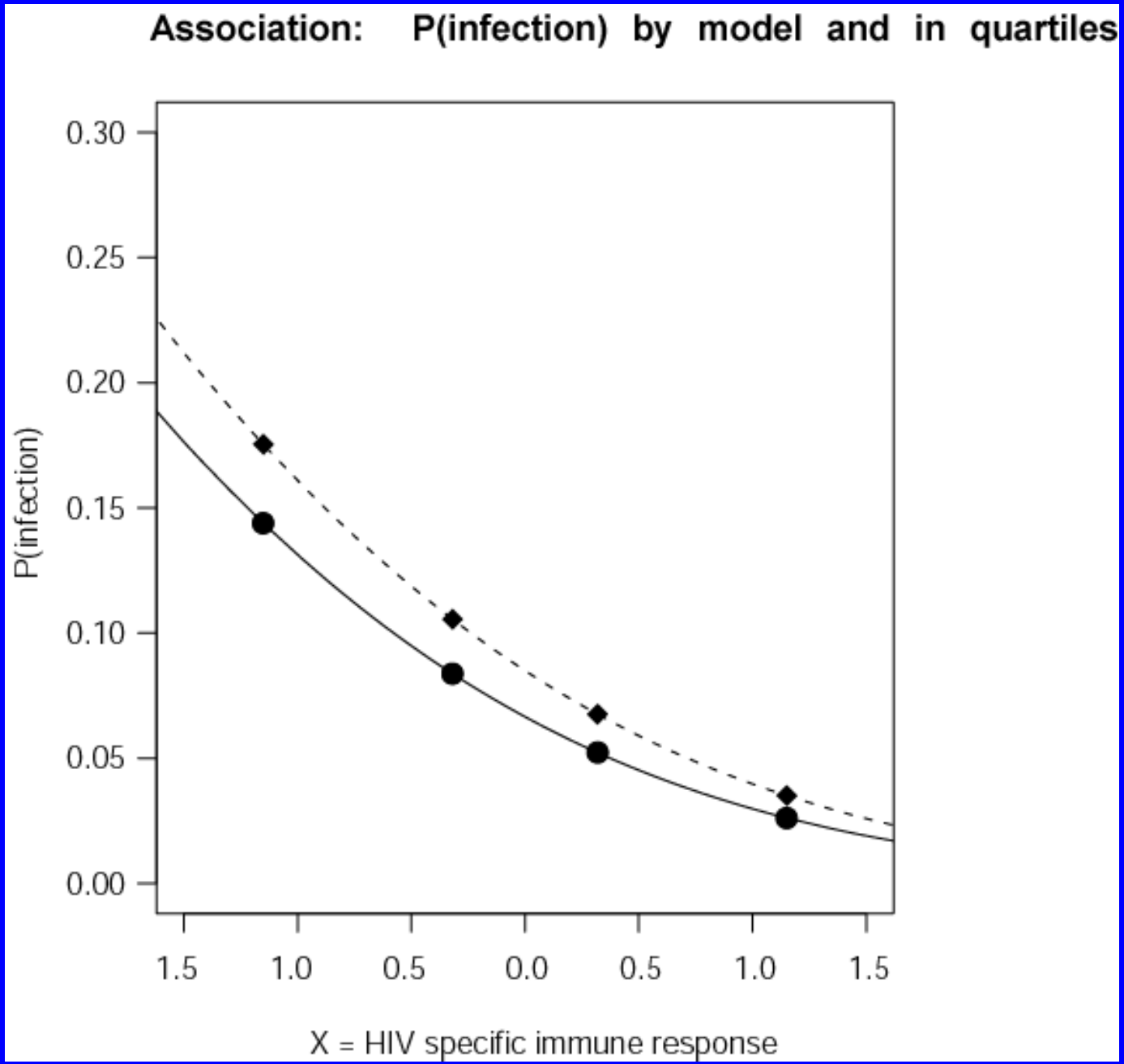
Maximum Likelihood

- 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

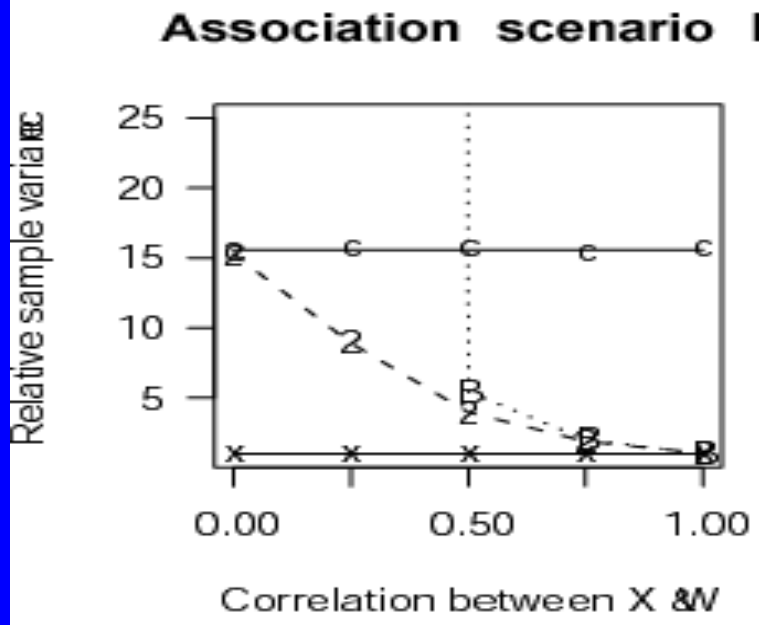

Causation: P(infection) by model and in quartiles
0.30
0.25
0.20
0.15
0.10
0.05
0.00
P(infection)
1.5
1.0
0.5
0.0
0.5
1.0
1.5
X = HIV specific immune response

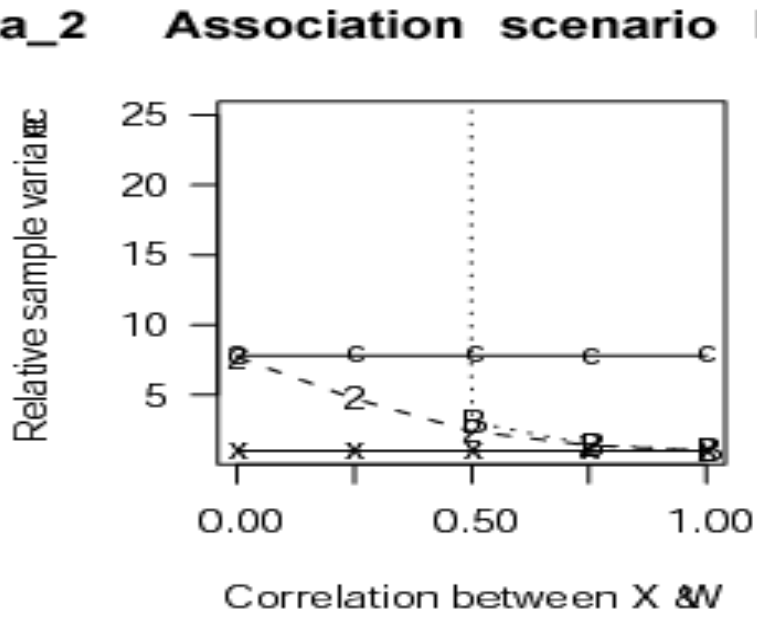

Association: P(infection) by model and in quartiles
0.30
0.25
0.20
0.15
0.10
0.05
0.00
P(infection)
1.5
1.0
0.5
0.0
0.5
1.0
1.5
X = HIV specific immune response

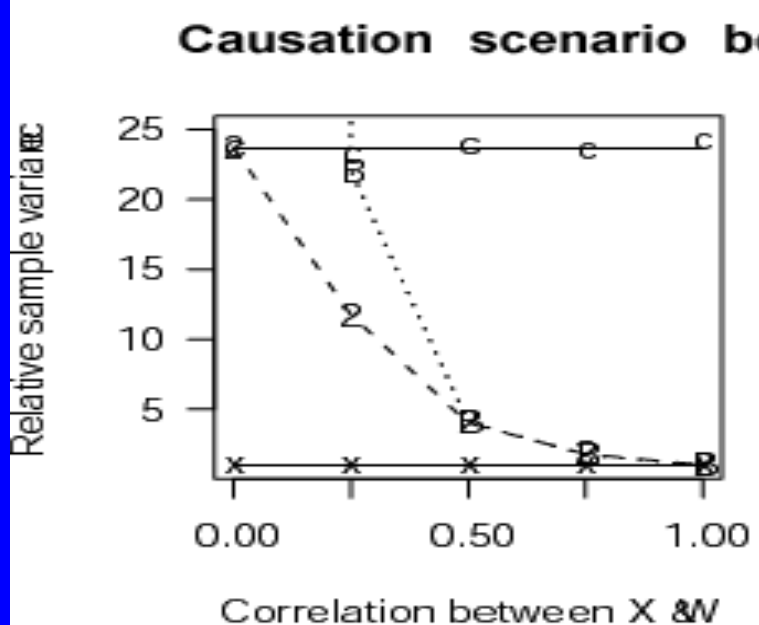
Results

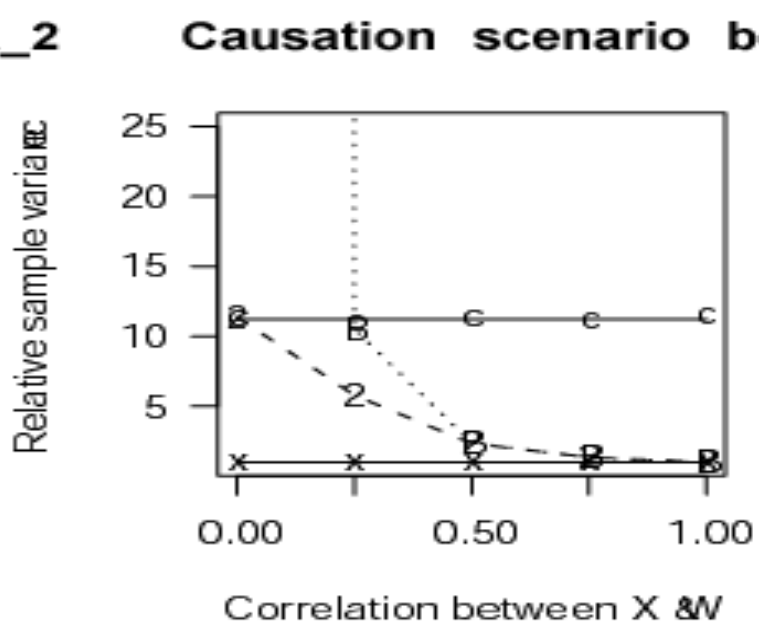
- Measure performance by sample variance.
- Association Scenario ρ =.5

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
Relative sample variance
25
20
15
10
5
0.00
0.50
1.00
Correlation between X &W


Association scenario beta_3
Relative sample variance
25
20
15
10
5
0.00
0.50
1.00
Correlation between X &W


Causation scenario beta_2
Relative sample variance
25
20
15
10
5
0.00
0.50
1.00
Correlation between X &W


Causation scenario beta_3
Relative sample variance
25
20
15
10
5
0.00
0.50
1.00
Correlation between X &W

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

- ρ =.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
- Michael Fay
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