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

<table>
<thead>
<tr>
<th>IMMUNE RESPONSE QUARTILE</th>
<th>GROUP</th>
<th>Weak</th>
<th>Modest</th>
<th>Good</th>
<th>Best</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>1.00</td>
<td>.43*</td>
<td>.34*</td>
<td>.29*</td>
<td></td>
</tr>
</tbody>
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* p<.05
## VAX004: Relative Risk of Infection Both Groups

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<tr>
<td>Placebo</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>1.00</td>
</tr>
<tr>
<td>Vaccine</td>
<td>1.67*</td>
<td>.98</td>
<td>.87</td>
<td>.74</td>
<td></td>
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* * 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 vs. Immune response to Rabies Vaccine

Placebo Group

Immune response to HIV Vaccine vs. 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

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<tr>
<td>Vaccine</td>
<td>Uninfected</td>
<td>70</td>
<td>85</td>
<td>90</td>
<td>95</td>
<td>340</td>
</tr>
<tr>
<td></td>
<td>Infected</td>
<td>30</td>
<td>15</td>
<td>10</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>400</td>
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Usual Trial Exploiting Randomization

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</tr>
<tr>
<td></td>
<td>Total</td>
<td>~100</td>
<td>~100</td>
<td>~100</td>
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<td>400</td>
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Trial with CPV (association)

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<tr>
<td></td>
<td>Infected</td>
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<td>~16</td>
<td>~8</td>
<td>~7</td>
<td>60</td>
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<td>~100</td>
<td>~100</td>
<td>~100</td>
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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:
    \[ P(Y = 1 \mid X) = \Phi(\beta_0 + \beta_2 X) \]
  – Vaccine Group:
    \[ P(Y = 1 \mid X) = \Phi(\beta_0 + \beta_1 + (\beta_2 + \beta_3) X) \]
Maximum likelihood estimation

• We need $X$ for $P(Y=1 \mid X, Z)$
  – Vaccine group, use $X_0$
  – Placebo Uninfected use $X_C$
  – Placebo Infecteds: Integrate $P(Y=1 \mid X, 0)$ 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
  \[ \Pi_{i \in V} p_v(x_{0i}) y(i) (1 - p_v(x_{0i}))^{1 - y(i)} \]
- Placebo contribution
  \[ \Pi_{i \in P(U)} (1 - p_p(x_{Ci}))^{1 - y(i)} \Pi_{i \in P(I)} p^*(w_i) y(i) \]
- \(x_{0i}, w_i\) 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: $P(\text{infection})$ by model and in quartiles

$X = \text{HIV specific immune response}$
Association: $P(\text{infection})$ by model and in quartiles

$X = \text{HIV specific immune response}$
Results

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

<table>
<thead>
<tr>
<th>Design</th>
<th>Variance of $\beta_2$ estimate</th>
<th>Relative Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPV</td>
<td>.0575</td>
<td>15.5</td>
</tr>
<tr>
<td>BIV</td>
<td>.0199</td>
<td>5.4</td>
</tr>
<tr>
<td>CPB+BIV</td>
<td>.0145</td>
<td>3.9</td>
</tr>
<tr>
<td>X known</td>
<td>.0037</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Performance depends on $\rho$

- 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

<table>
<thead>
<tr>
<th>$\beta_2$</th>
<th>$\beta_3$</th>
<th>Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>.86/.1.00</td>
<td>.03/.05</td>
<td>Association</td>
</tr>
<tr>
<td>.04/.05</td>
<td>.78/.99</td>
<td>Causation</td>
</tr>
<tr>
<td>.57/.95</td>
<td>.35/.65</td>
<td>Both</td>
</tr>
</tbody>
</table>
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
• Cliff Lane
• Ed Tramont